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The American Heart Journal

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Original Communications

A CLINICAL TYPE OF PAROXYSMAL TACHYCARDIA OF VENTRICULAR ORIGIN IN WHICH PAROXYSMS ARE INDUCED BY EXERTION*

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INTRODUCTION

PATIENTS who are subject to simple paroxysmal tachycardia, paroxysmal flutter, or paroxysmal auricular fibrillation not infrequently describe individual attacks that were precipitated by exertion or excitement. Ordinarily the attacks are separated by comparatively long intervals of time and cannot be induced at will. Rest has little or no effect upon the duration of the abnormal rhythm.

It is our purpose to call attention to a type of paroxysmal tachycardia of ventricular origin in which moderate exertion invariably or almost invariably brings on an attack. While long attacks lasting several hours or days sometimes occur, a rapid succession of short paroxysms is more usual. In the pauses between these short attacks ventricular extrasystoles occur singly or in salvos of two to five or more. Rest is often followed by a gradual decrease in the length and frequency of the paroxysms and the return of normal rhythm. From a clinical standpoint this condition is quite different from paroxysmal tachycardia of the ordinary type. It may be easily overlooked. Many of the patients subject to it show no signs of structural heart disease and no disturbance of the cardiac mechanism while at rest. A complaint of palpitation on exertion or the discovery of an extrasystolic arrhythmia arouses no suspicion that a serious cardiac disorder is present, and it is only when the patient is examined after exertion that the real nature of the disorder is discovered.

In France there has been a tendency, particularly evident in the writings of Gallavardin and his associates,[1, 2, 3, 4, 5] to divide paroxysmal tachycardia into a number of clinical types, which may or may not differ fundamentally. According to Gallavardin[4, 5] attacks of paroxysmal

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tachycardia of the classical type (*Tachycardie paroxystique type Bouveret*) are not as a rule preceded or followed by extrasystolic arrhythmia. When isolated extrasystoles do occur in association with the onset or termination of the paroxysms, they are not of the same electrocardiographic type as the beats that constitute the rapid rhythm, and this rhythm is not regarded by Gallavardin as necessarily due to a succession of extrasystoles. In this type of paroxysmal tachycardia the attacks are, as a rule, relatively long and rather infrequent. Gallavardin has, however, described a group of cases of paroxysmal tachycardia of supraventricular origin in which the attacks were extremely frequent and were easily provoked by exertion and excitement.[3] In these cases false arrest often occurred; i. e., the rapid rhythm was frequently interrupted by short periods of normal mechanism. Gallavardin[5] apparently regards cases of this kind as a distinct variety of paroxysmal tachycardia of the classical type in which the paroxysmal center is unusually excitable; he refers to them as examples of "*Tachycardie paroxystique à centre excitable.*"

He considers paroxysmal tachycardia in which the attacks are preceded or followed by isolated extrasystoles of the same electrocardiographic type as the beats which constitute the ectopic rhythm as belonging to an entirely different group;[4, 5] "*L'extra-systolie à paroxysmes tachycardiques.*" In the majority of the cases of this group the abnormal rhythm consists in a succession of short paroxysms lasting from a few seconds to one or two minutes (*tachycardie en salves*) separated by periods in which beats of normal origin are interspersed with extrasystoles occurring singly, in pairs, or in short runs. In rare cases the paroxysms are very long, and Gallavardin[4] has reported an instance in which the abnormal rhythm persisted continuously for a period of thirty days. At the beginning and toward the end of this period, however, the tachycardia was occasionally interrupted by the occurrence of beats of normal origin.

It will be seen that the cases described in this article correspond, on the one hand, to the cases referred to by Gallavardin as *tachycardie en salves*, and, on the other, to the group which he designates *tachycardie paroxystique à centre excitable.*

ILLUSTRATIVE CASES

Case 1.—An American farmer, aged thirty-one years, was admitted to the University Hospital, August 29, 1924, complaining of breathlessness, and attacks of rapid heart action.

***Present Illness.*—He had always been well and had had an unusual capacity for work until December 29, 1917. On that date while he was chopping wood, his heart suddenly began to beat with extreme rapidity and violence. He felt a "buzzing" in his chest, and was soon covered with cold perspiration. He was very weak and lay down on a log, but, after a few minutes, got up and managed to reach his home, a half mile away. On entering the house he sat down on a couch and suddenly became unconscious, remaining so for "about one hour." When he regained consciousness, the heart action was normal. A second attack occurred one week later, when he**

learned through a neighbor that his physician thought that he would not live long. He remained in bed for six weeks and was then taken to a hospital for a fortnight. While in the hospital he was given spartein, and he continued this drug for about one year after returning home. During this time he was frequently short of breath, but he had no more attacks until December, 1918, when a paroxysm came on while he was hunting rabbits in deep snow. He could not walk home, but had to be brought to the house with a horse and wagon. The rapid heart action continued for three or four hours. From that time the attacks were so frequent that he was almost completely incapacitated by them. They were usually brought on by exertion, eating, or excitement. They varied in duration from a few seconds to seven days. He took many kinds of drugs, including spartein, which had previously seemed to give him relief, without effect. On several occasions he became unconscious for a brief interval, and he believed that each time the fainting spell occurred just after the paroxysm came to an end. The cessation of the rapid heart action was often followed by nausea and vomiting.

Past History.—He had had a severe attack of scarlet fever without complications at thirteen years, a severe attack of pneumonia at seventeen, and a light attack of influenza in 1918. Several years before his illness he had a perirectal abscess which healed after drainage. He gave no history of rheumatic fever, chorea, or tonsillitis and denied having had venereal disease. The marital and family history were not significant.

On examination, the patient was well developed, and well nourished. There was no cyanosis and no objective dyspnea; no congestion of the neck veins, or throbbing of the peripheral arteries. The radial and brachial arteries were slightly thickened but not tortuous or beaded. There was no tracheal tug, substernal dullness, or pulsation in the suprasternal notch. There was no heaving of the precordia. The left border of the heart could not be definitely located by inspection or palpation, but the left border of cardiac dullness was about two centimeters outside the nipple line. At the apex, the heart sounds were rather distant. At the base, the aortic second sound was slightly accentuated. There were no murmurs. The rhythm was disturbed by frequent extrasystoles, and bigeminy was present for brief periods. The examination of the abdomen and the extremities was entirely negative.

Laboratory Tests.—An x-ray examination of the chest showed nothing abnormal in the lung fields. The size of the heart was difficult to make out because of the presence of scoliosis, but the teleroentgenogram showed a Danzer ratio of 0.49. The examination of the urine and of the blood showed no abnormalities. The systolic blood pressure was 130 mm. Hg, and the diastolic 69 mm. Hg. The Wassermann test was negative.

Special Studies.—An electrocardiogram taken on September 2 showed pronounced V-shaped inversion of the T-deflections in Leads II and III and bigeminy due to ventricular extrasystoles. The form of the extrasystolic complexes was exceedingly variable. An electrocardiogram taken on September 4 (Fig. 1) was similar in all respects except that no extrasystoles were present. Exertion (running up and down stairs) induced bigeminy and multiple extrasystoles, as many as six in succession; the form of the extrasystolic complex was again variable. As a rule no two extrasystoles of a succession were alike in form or spacing. After the exercise had been repeated several times, however, a long attack of paroxysmal ventricular tachycardia was precipitated. The paroxysmal rate was about 200 per minute and the rhythm slightly irregular. The inhalation of amyl nitrite had no effect upon the cardiac mechanism. Three grains of quinidine were given and the attack stopped suddenly about twenty-five minutes later. In the later stages of the attack the rate varied; it rose as high as 243 per minute and fell as low as 165 per minute.

On September 5 an attack came on spontaneously while the patient was using a bed pan. It stopped after fifteen or twenty minutes. Vagus pressure was without

effect. On this date attacks could be induced at will by exertion. The paroxysmal rate varied from 171 to 231. Two paroxysms separated by a single normal beat differed in rate by 32 beats per minute (Fig. 2). The rhythm was sometimes conspicuously irregular (Fig. 2) during the paroxysms; at other times the irregularity was very slight (Fig. 1). From September 6 to 10 the patient was given quinidine sulphate; 0.4 gm. at 8:30 A.M.; 0.2 gm. at 11:30 A.M. and at 3:30 P.M. During this period he was free of attacks not only while in bed but also while he was walking about. He asserted that he had not felt so well in months. Attacks could still be induced by exertion, and extrasystoles were frequently present. Quinidine was dis-

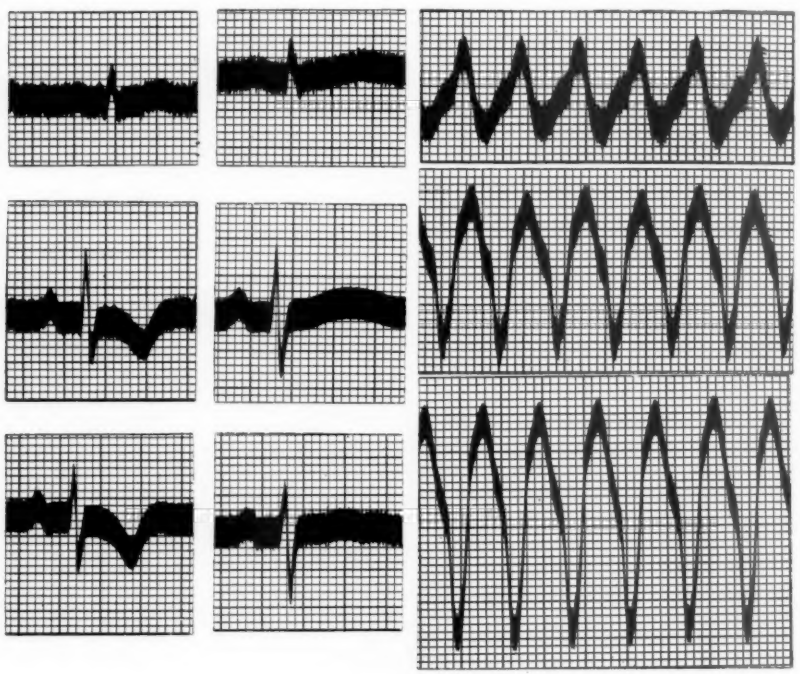

Fig. 1.—Case 1. Left-hand column: Leads I, II and III in order. Taken on September 4, 1924. The T-deflections are sharply inverted in Leads II and III.
Center column: Leads I, II and III in order. Taken on September 8, 1924, when the patient was receiving 12 grains of quinidine sulphate per day. The T-deflections are now upright.
Right-hand column: Leads I, II and III in order. Taken on September 5, 1924, during a long attack of ventricular tachycardia. Heart rate 212 per minute. There is no definite arrhythmia. (In all tracings a deflection of 1 cm. represents a potential difference of 1 millivolt.)

continued on September 9, but no paroxysms occurred until September 12. On this date the electrocardiogram showed frequent auricular extrasystoles as well as ventricular extrasystoles. Eight to ten auricular extrasystoles sometimes occurred in succession (Fig. 3). The patient had several attacks of paroxysmal ventricular tachycardia, and these were frequently interrupted by runs of auricular extrasystoles (short attacks of paroxysmal auricular tachycardia) which occurred at a slightly more rapid rate than the beats of the ventricular paroxysm and therefore temporarily suppressed the ventricular pacemaker (Fig. 3). When the rates of the paroxysmal auricular center and of the paroxysmal ventricular center were nearly the same, interference took place, and the ventricular complexes were transitional in form between the complexes of the paroxysmal auricular and those of the paroxysmal ventricular series (Fig. 3).

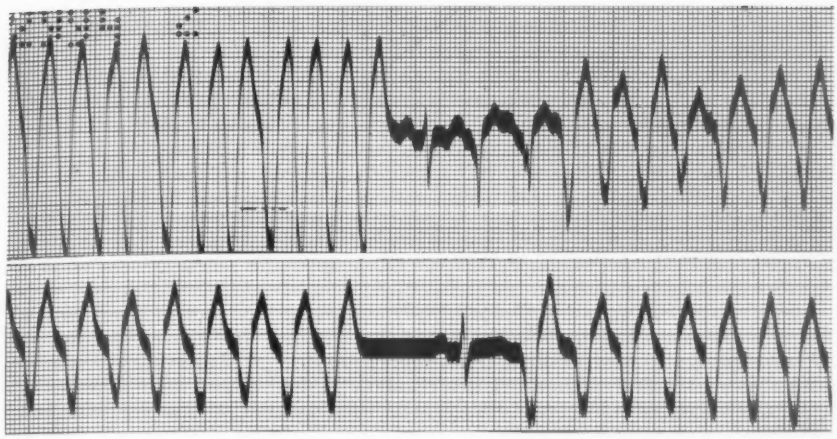

Fig. 2.—Case 1. Upper curve: Lead III showing the end of one attack of ventricular tachycardia and the onset of another (September 5, 1924). The rhythm was definitely irregular during the paroxysms. During the first paroxysm the rate was approximately 220 per minute; during the second, approximately 188 per minute.

Lower curve: Lead III, taken September 12, 1924. Two paroxysms of ventricular tachycardia are separated by a single beat of sinus origin. During the first paroxysm the heart rate was approximately 178 per minute; during the second, approximately 183 per minute. The interval which separates the last beat of the first paroxysm from the first beat of the second (1.48 second) is not an exact multiple of the paroxysmal cycle length which averages 0.337 second for the first paroxysm and 0.328 second for the second.

Fig. 3.—Case 1. All tracings taken September 12, 1924. Lead III only. Top tracing: Short runs of auricular extrasystoles, usually preceded by one or two ventricular extrasystoles.

Middle tracing: An attack of ventricular tachycardia temporarily interrupted by a short run of auricular extrasystoles occurring at a slightly more rapid rate than the beats of ventricular origin (the rate was approximately 185 per minute in both cases). At the onset of the auricular paroxysm complexes of transitional form due to interference are seen. Measurements of the length of a number of periods of interruption of this type indicate that the auricular impulses often reached the ventricular center and brought the ventricular paroxysm temporarily to an end.

Lower tracing: Two short runs of complexes of transitional form temporarily interrupting a ventricular paroxysm. These transitional complexes are due to interference between the ventricular center and an auricular center producing paroxysms of stimuli at approximately the same rate. An auricular complex is superimposed upon the T-wave of each of these transitional complexes except the last of each group.

The administration of quinidine was resumed on September 13 and continued during the remainder of the patient's stay in the hospital. One attack lasting thirty minutes occurred on this date and a few short attacks on the following day, but he was comfortable thereafter. Exertion failed to produce a long attack on September 13 and again on September 18, although many short attacks consisting of five or six beats in succession did occur (Fig. 4). Atropin (one twenty-fifth of a grain intravenously) on September 13 had no definite effect upon the frequency of the abnormal beats. The inverted T-deflections present on admission gave place to broad upright waves when quinidine was given (Fig. 1) and returned when this drug was omitted.

The patient was discharged on September 24. We have since learned that he was able to return to work but died suddenly while eating lunch a few months after he left the hospital. No further details could be obtained.

CASE 2.—An American plumber, aged fifty-two years, was admitted to the hospital October 24, 1929, complaining of shortness of breath and palpitation.

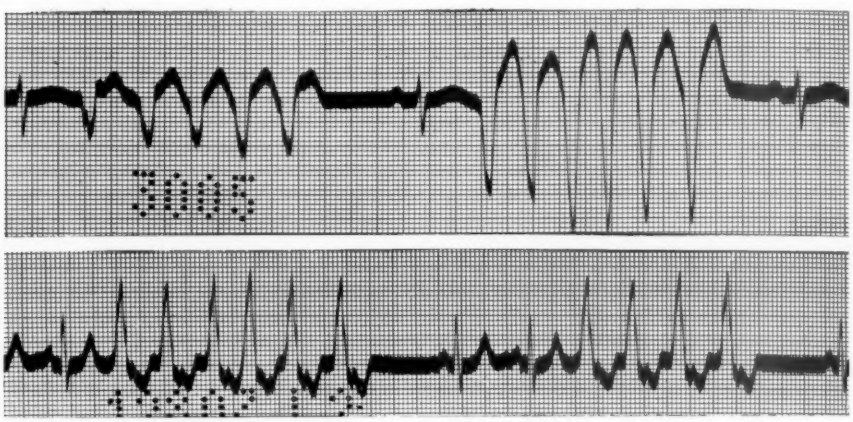

Fig. 4.—Upper tracing: Case 1, Lead III. Taken on September 18, 1924. At this time the patient was receiving 9 to 12 grains of quinidine sulphate per day. Exertion precipitated only short runs of ventricular extrasystoles; no long attacks.
Lower tracing: Case 4, Lead II. Short paroxysms of ventricular tachycardia occurring in rapid succession. The auricles responded to the ventricles during the paroxysms.

Present Illness.—He was entirely well until August, 1927, when he had an attack of palpitation after eating which lasted one or two hours and produced slight dizziness. A second attack occurred two weeks later and four or five other attacks during the remainder of the year. At the onset of these later attacks he noticed a choking sensation and a feeling of pressure in the region of the ensiform. During the attacks he felt faint; he had a beating sensation between the eyes and a "wooden" feeling in the head. He would forget things that he had heard only a few minutes before.

In January, 1928, he became short of breath and had to give up work. Sweeping or any other slight exertion would bring on an attack which might last eight to ten hours. He had to lie down most of the time because of giddiness and faintness. Occasionally he had sharp shooting pains in the precordia with dull pain in the left shoulder, but without radiation to the arm. These pains were not relieved by nitroglycerin.

In June, 1928, he was at his worst; slight exertion such as walking up a few steps would precipitate an attack. He had frequent fainting spells and often felt as though he were going to die. During an attack he could hardly feel his heart beating. In January, 1929, he began to improve and had since felt much better, but still had

frequent attacks and was unable to work. He had gained about ten pounds in weight. He had never suffered from orthopnea or cough. He had had no edema of the ankles.

The *past history* threw no light upon the etiology of the cardiac disorder. He had had the usual diseases of childhood but no scarlet fever, chorea or rheumatic fever. He denied venereal disease and had seven children living and well.

Physical Examination.—The patient was well developed and slightly obese. His complexion was ruddy and he did not appear ill. The skin, head, ears, eyes, and nose showed nothing abnormal. The teeth were artificial. The tonsils were slightly enlarged. There was no thyroid enlargement. The lungs were normal. The cardiac apex was felt in the fourth intercostal space 9 cm. from the midline. The area of cardiac dullness was not increased. There were no murmurs. The blood pressure was 150/90 mm. Hg. The abdomen and the extremities were negative.

Laboratory Tests.—On x-ray examination the heart was thought to be slightly

Fig. 5.—Case 2. Time in fifths of a second. Two leads taken simultaneously.
Upper left curve: Leads I and II before exercise (October 28, 1929). Normal electrocardiogram.
Upper right curve: Leads I and III after exercise (November 6, 1929). A short paroxysm of ventricular extrasystoles arising at one center interrupted by a single ventricular extrasystole arising at a second center. During the paroxysm the auricles responded to the ventricles.
Lower curve: Leads I and III after exercise (October 28, 1929). A period of extrasystolic bigeminy followed by a paroxysm of ventricular tachycardia. Measurements of curves of this type indicate that in general the interval between two successive extrasystoles was not an exact multiple of the paroxysmal cycle length. Unfortunately, the ventricular rhythm was often somewhat irregular so that too much stress should not be laid upon this point.

enlarged to the right and the aorta appeared to be somewhat tortuous and slightly dilated. The Wassermann test was negative. The blood and urine were normal. The basal metabolic rate was 17 per cent below normal on two occasions.

Special Studies.—An electrocardiogram taken on October 14 was normal in every respect; the heart rate was 60 per minute. On October 18 the patient complained of pain in the precordia and irregular heart action. In the electrocardiogram every second normal complex, at times every normal complex, was followed either by a single extrasystole or by a series of from two to five, usually four, occurring in rapid succession. All of the extrasystoles were represented by complexes of the same type. The irregularity persisted for two or three hours.

At 9:40 A.M. on October 21 the electrocardiogram was normal and the heart rate was 69 per minute. Mild exertion (walking rapidly up and down a flight of stairs) sufficient to raise the sinus rate to 125 per minute was followed by a series

of short attacks of paroxysmal ventricular tachycardia separated by brief periods of bigeminy or trigeminy. The paroxysmal rate varied in different attacks from 166 to 184 per minute. When the patient rested, the disturbance gradually subsided, but returned on further exertion. It was observed that the paroxysms did not as a rule begin during the exercise but one or two minutes after it had been completed. Attacks were also induced by exertion on October 22.

On October 23 the patient was given a single dose of quinidine sulphate (0.8 gm.) at 1 P.M. At 2:35 P.M. the electrocardiogram was normal and the heart rate 73 per minute. The T-deflections were slightly flatter and broader than on previous occasions (quinidine effect). Paroxysms were induced by exertion several times during the afternoon; it seemed slightly more difficult to precipitate them than it had been previously. The paroxysmal rate varied from 168 to 188 per minute. No relation could be discovered between the paroxysmal rate and the sinus rate just before or just after the paroxysm.

From October 24 to November 1 the patient was given 0.4 gm. of quinidine sulphate three times per day. During this period he was comfortable and had no spontaneous attacks. At 3 P.M. on October 28 the electrocardiogram was normal (Fig. 5) and the heart rate 60 per minute. Exertion raised the sinus rate to 100 per minute and again produced paroxysms similar to those previously described (Fig. 5). Exertion also produced paroxysms on October 31; abnormal heart action persisted for eight minutes. Euphyllin 0.1 gm., three times per day, was substituted for quinidine on the morning of November 1. On the following morning walking up and down three flights of stairs four times (an amount of exertion not greater than that previously employed to induce attacks) was followed by a succession of paroxysms which began about one minute after the completion of the exercise and continued for five and one-half hours. Amyl nitrite had no effect. As many as 43 extrasystoles in succession were counted. While taking euphyllin the patient had frequent spontaneous attacks and also complained of nausea. When this drug was replaced by quinidine, he was again comfortable and practically free of extrasystoles so long as he remained quiet.

The patient was discharged on November 18, 1929. A recent letter (April, 1932) from his home physician (Dr. D. Pierpont of Ironwood, Michigan) states that he is feeling much better than when he left the hospital and can walk a mile without much discomfort, but is not able to work. His pulse rate is usually between 60 and 65 per minute. He has substernal pain at times especially on climbing stairs. A letter from the patient (April, 1932) states that he has not had a heart attack for about six months. He has substernal pain on exertion, but if he continues the exertion the pain subsides.

CASE 3.—We have had the opportunity of making less complete observations on a third example of this disorder. The patient was a woman in the late thirties. She had had typhoid fever but no other serious illnesses. There was no history of chorea or rheumatic fever. For several years she had noticed pronounced palpitation induced by exertion or excitement. There were no other symptoms except a rather marked feeling of exhaustion which varied greatly in intensity. The examination of the heart revealed no signs of structural disease. The thyroid gland was slightly enlarged but there were no symptoms or signs of thyroid intoxication. The remainder of the examination was negative. The electrocardiogram was normal when the patient was resting. Immediately after exertion each normal beat was followed by a succession of four to ten ventricular extrasystoles. In the course of a few minutes the extrasystolic salvos became less frequent, the number of extrasystoles in each group decreased and normal rhythm was established. The amount of exertion necessary to precipitate the disordered heart action was very small, and the patient found it practically impossible to do any type of work involving physical effort or

excitement. Quinidine sulphate (0.2 gm. two or three times a day) lessened the frequency of the attacks but did not abolish them.

CASE 4.—A fourth patient (male, aged twenty-five years) whom we have seen only once, displayed a similar disturbance of the cardiac mechanism, but in this instance there was no definite relation between exertion or excitement and the attacks. He complained of an increased tendency to fatigue during the preceding three years and of palpitation. The past history was negative. The examination revealed nothing abnormal except slight scoliosis, very mild anemia, and cardiac arrhythmia. There were no signs of structural heart disease. In the electrocardiogram every second normal beat was followed by a series of from two to seven ventricular extrasystoles (Fig. 4). Each ectopic impulse, except perhaps the first of each series, was conducted to the auricles. This is indicated not only by the notch on the downstroke of the inverted T-waves but also by the uniform length of the post paroxysmal pause (Fig. 4). There was no change in the cardiac mechanism during the few hours that the patient was under observation.

SIMILAR CASES DESCRIBED IN THE LITERATURE

We have not made an exhaustive study of the literature, but in a brief survey of the publications of recent years relating to paroxysmal tachycardia we have found a number of case histories similar to those given above.

The patient studied by Scott[6] was a woman, aged thirty-nine years, who gave a history of typhoid fever and of vague rheumatic symptoms at twenty-two years of age. She had suffered from palpitation for about ten years. At first the attacks were not frequent or severe, and they gave her no particular concern. For the past year, however, she had been unable to work. Attacks of rapid heart action were easily precipitated by exertion and lasted from one to forty-eight hours. There was no evidence of structural heart disease, the blood pressure was normal, and the Wassermann test negative. Mild cardiac failure occurred in the longer attacks. The electrocardiograms were similar in all respects to those obtained in our cases. The abnormal beats arose in the ventricles and were conducted to the auricles. The effect of drugs was very carefully investigated. Nitroglycerin had no effect. Both atropine (0.02 to 0.03 grain) and adrenalin (10 to 15 minims of a 1: 1000 solution intramuscularly) precipitated attacks. Long attacks could invariably be brought to an end by a single dose of quinidine sulphate (0.4 gm.). When quinidine was given regularly (0.2 gm. three times per day), the patient was free of attacks and was able to return to work. When the drug was discontinued some six months later the attacks returned, but they stopped again when the administration of the drug was resumed. We are informed (May, 1932) by Dr. Scott that this patient has recovered completely. She no longer takes quinidine and has had no attacks for several years. Examination of the heart shows nothing abnormal.

Two cases are briefly described by Wenckebach and Winterberg[7] in their book on irregular heart action. The first patient was a woman forty-four years of age, who complained of severe palpitation on exertion. When she was at rest the cardiac rhythm was sometimes normal, sometimes disturbed by ventricular extrasystoles occurring singly or in groups of two to three. Mild exertion increased the frequency of the abnormal beats. More violent exertion was followed by short attacks of paroxysmal ventricular tachycardia. On one occasion the cardiac rhythm was normal and the heart rate 60 per minute. Exertion induced an attack which lasted for twelve minutes. At the onset the paroxysmal rate was 230 per minute, but in two minutes it had fallen to 183 where it remained until the paroxysm ended. The end

of this attack was followed by salvos of extrasystoles, and normal rhythm was only gradually reestablished.

The second patient was a woman, aged fifty-three years, who had always been well except for rheumatic fever twenty-eight years before. Three years before she began to have palpitation on exertion, and the amount of exertion necessary to induce this symptom had gradually diminished. When the patient was resting the cardiac mechanism was normal and the heart rate was 60 per minute. Exertion invariably induced attacks of ventricular paroxysmal tachycardia, and spontaneous attacks were also observed. After mild exertion the tachycardia began at once, but after more violent exertion there was a delay of one or two minutes. Electrocardiograms showed that this delay was due to the very rapid sinus rate. When the sinus rate was driven above the usual paroxysmal rate, the abnormal heart action did not begin until the sinus rate had fallen to the paroxysmal level. When this point was reached, interference between the two rhythms with ventricular complexes of transitional form occurred at the onset of the abnormal rhythm.

Anderson's[8] patient was a boy aged seventeen years who complained of frequent attacks of palpitation during the previous three years. Attacks were induced by excitement and exertion but also occurred spontaneously. There was no history of rheumatic fever, chorea, scarlet fever, or diphtheria, and there were no signs of structural heart disease. At first the abnormal cardiac mechanism consisted in a rapid succession of short runs of ventricular extrasystoles, but later long attacks occurred. When taking quinidine (5 grains morning and evening) the patient was completely free of attacks. The discontinuance of this drug was followed by a period during which attacks could be induced by exertion, although the isolated extrasystoles that were usually numerous just before and just after an attack were entirely absent. At the beginning of one attack studied the auricles beat independently, but later the auricular rate was exactly one-half the ventricular.

Cases 4 and 5 of the series of cases of paroxysmal tachycardia reported by Gilchrist[9] also belong to the group under consideration. The first of these patients was a man aged forty-one years who complained of short attacks of palpitation brought on by exertion. The heart was slightly enlarged to the left, but there were no other signs of structural heart disease. Aside from a secondary anemia the remainder of the clinical examination was negative. The patient was in the habit of smoking large quantities of strong tobacco.

When normal rhythm was present, the electrocardiogram showed very large inverted T-waves (Lead III), similar to those which occurred in our Case I. An electrocardiogram taken during an attack showed a very irregular succession of strikingly abnormal ventricular complexes. No auricular waves were visible. Alternation in the form of the ventricular complexes is seen at the beginning of one of the small strips of record reproduced.

The second patient, a man aged nineteen years, had suffered from attacks of giddiness and weakness for the past eighteen months. These attacks were precipitated by exertion. At first they lasted only four or five minutes, but more recently attacks lasting two or three hours had occurred. An electrocardiogram taken during an attack showed "an intimate mixing of short ventricular paroxysms, multiple and isolated extrasystoles, and occasional beats of normal origin." There was no evidence of structural heart disease. Attacks were easily induced by exertion. When taking seven grains of quinidine per day the patient was free of attacks and able to work. Vagal stimulation and large doses of digitalis had no effect upon the abnormal cardiac mechanism. In one of the tracings published the paroxysmal rhythm is nearly regular; a second tracing shows a very high grade irregularity.

The patient studied by Allan[10] was a man aged fifty-three years who complained of short attacks of giddiness and faintness which had occurred off and on for the past

twelve years. Recently these attacks had become more frequent; the patient was convinced that exertion and excitement precipitated them. In some attacks he became unconscious, and typical Stokes-Adams seizures were observed while he was in the hospital. Between attacks the examination of the heart was entirely negative and the electrocardiogram was normal. Electrocardiograms taken during attacks showed runs of ventricular extrasystoles varying in duration from six to twenty-three seconds. Extrasystoles of the same type as those of the paroxysmal series occurred singly or in pairs between the periods of rapid rhythm. After the first few beats of the ectopic rhythm the auricles responded to every second ventricular contraction. Quinidine sulphate (0.2 gm. one to three times a day) completely abolished the attacks.

Hume[11] reported six cases of paroxysmal tachycardia occurring in soldiers in France. In four of these cases attacks were induced by exertion. They could not be induced by the administration of atropine (one-thirtieth grain) or adrenalin (two and one-half minims of a 1: 1000 solution intravenously). None of the patients showed any evidence of structural heart disease. It was impossible to be certain that the attacks were ventricular in origin.

Willius[12] reported a series of five cases of paroxysmal ventricular tachycardia. He states that the attacks were related to exertion and excitement but gives no details.

COMMENTS

The most notable features of the group of cases under consideration are: (a) the relation of the attacks to exertion and excitement; (b) the absence in the majority of the cases of signs of structural heart disease; (c) the occurrence of many short attacks in rapid succession separated by periods of high grade extrasystolic arrhythmia; and (d) the effectiveness of quinidine in controlling the abnormal mechanism.

Because of the relation of the paroxysms to effort and emotion the attacks are exceedingly frequent and the patient is usually seriously handicapped. As a rule the disability is greater than that produced by a well-compensated valve lesion or by continuous auricular fibrillation without congestive failure. In those cases that have been followed for a considerable period of time there has been with one exception (Scott's case) little tendency to recovery. The frequent occurrence of ventricular paroxysmal tachycardia in coronary thrombosis and the relation of the pain of angina pectoris to effort and excitement suggest the possibility that coronary disease may be the cause of this disorder. There is, however, little evidence to support this view. It is not in harmony either with the youth of some of the patients or with the absence of clear evidence of structural heart disease in the majority. Typical anginal pain did not occur in any of the cases reviewed. In the case histories evidence of general arteriosclerosis, arterial hypertension, diabetes, and luetic infection, all of which are relatively common in cases of coronary disease, is conspicuously absent. It may be pointed out, however, that in one of our cases and in one of those reported by Gilchrist the T-deflections of the electrocardiogram were strikingly inverted in Leads II and III when the cardiac mechanism was normal. T-deflections of this type appear to be relatively frequent in cases of ventricular paroxysmal tachycardia

and are somewhat similar to the T-wave changes that are seen in coronary thrombosis. They evidently indicate a local change in the duration of the excited state in the ventricular muscle. Such a change may depend either upon a structural lesion or merely upon altered function dependent perhaps upon influences exerted by the vegetative nervous system. It is noteworthy that quinidine may profoundly alter the form of these inverted T-deflections (Case 1).

The relation of the attacks to exertion and excitement, the absence of signs of structural heart disease, and the fact that paroxysms are precipitated in some of the cases by adrenalin and atropine suggests that the cause of the disorder may lie in the vegetative nervous system rather than in the heart. Attacks appear to be induced in susceptible individuals chiefly by procedures that increase accelerator or diminish vagal tone. It is worthy of note, however, that none of the patients studied displayed any evidence of thyrotoxicosis. The abnormal mechanism is not very unlike that which Levy[13] produced in animals under light chloroform anesthesia by the injection of adrenalin, nicotine, atropine, and other drugs and by direct or reflex sympathetic stimulation. Levy found that after removal of the adrenal glands and the sympathetic nerve supply to the heart these disturbances of the heart beat could no longer be induced by sympathetic stimulation; the injection of adrenalin still induced them. Beattie, Brow and Long[14] found that they could be prevented by section of the hypothalamus so long as the adrenal medulla was inactive. It is possible that in patients who display the type of paroxysmal tachycardia under consideration the heart is for some unknown reason unusually susceptible to sympathetic stimulation as it appears to be in the early stages of chloroform anesthesia.

Paroxysmal tachycardia of the classical type may usually be recognized from the patient's description of the sudden onset and termination of the attacks. Where the attacks are short and frequent and are preceded and followed by high grade extrasystolic arrhythmia, this is no longer possible and it is not easy to determine the true nature of the difficulty unless the patient is seen during an attack.

Quinidine may be regarded as a specific remedy in this disorder in the same sense as digitalis is so regarded in auricular fibrillation; i. e., the benefit derived by the patient is comparable in the two cases. In some instances small doses of this drug completely prevent the occurrence of attacks and enable the patient to return to his customary mode of life. In others, doses that are easily tolerated when taken over long periods of time are not sufficient to prevent attacks altogether, but seem to decrease their frequency and severity. These effects of quinidine are not, however, peculiar to the type of paroxysmal ventricular tachycardia described in this article; similar results occur in all types of paroxysmal ventricular tachycardia with the possible exception of the type that occurs in digitalis intoxication.

Certain features of the cardiac mechanism in the cases described are worthy of brief comment. In Case 1 there was evidently some region within the junctional tissues that was capable of conducting impulses from auricles to ventricles, but not in the reverse direction. During the paroxysms of ventricular tachycardia the sinus node continued to function as auricular pacemaker. In some of the shorter attacks the auricular complexes could be identified without difficulty; in the longer attacks this was not possible, but the frequent absence of a postparoxysmal pause when the termination of the abnormal rhythm was recorded indicates that the auricular rhythm was not disturbed by the ventricular tachycardia. The more or less regular occurrence in many of the records of isolated ventricular complexes transitional in form between the paroxysmal complexes and the complexes of supraventricular origin strongly suggests that from time to time during the paroxysms impulses of sinus origin reached the ventricles. The unidirectional block in the junctional tissues was not due to a general depression of atrioventricular conduction with a slightly greater depression of conduction from ventricles to auricles than of conduction in the opposite direction. When an auricular tachycardia occurred during a ventricular paroxysm and the auricular rate exceeded the ventricular the ventricles responded to the auricles, and there was no indication that conduction in the forward direction was in any way subnormal (Fig. 3). In Case 2 conduction took place with equal or almost equal facility in either direction; the auricles responded to the ventricles during the paroxysms, and even single ventricular extrasystoles were followed by sequential auricular beats (Fig. 5).

These cases furnish no data that enable us to come to any final decision regarding the nature of the abnormal mechanism, and a full discussion of all of the possibilities would prolong this article beyond a reasonable length. We may, however, point out a few difficulties that are encountered when an attempt is made to interpret them in terms of the views with respect to paroxysmal tachycardia that are now most widely held. If the ventricular paroxysms are attributed to circus contraction and the isolated extrasystoles are regarded as re-entrant beats, it is difficult to understand what took place when, as in Case 1 and in one of the cases described by Wenckebach and Winterberg, a portion of the ventricular muscle responded to the paroxysmal center and a portion to stimuli that descended from the auricles, or when the paroxysmal rhythm was temporarily interrupted by a more rapid rhythm of supraventricular origin (Fig. 3). If the paroxysmal rhythm was indeed a circus rhythm, one must assume that the interfering stimuli did not penetrate to the ring of muscle traversed by the re-entrant wave. This assumption places serious limitations upon the size of this ring and involves further assumptions of questionable validity regarding the rate of conduction about it or the length of the refractory period of the muscle of which it was made up. When the ectopic rhythm was interrupted temporarily, the

interfering stimuli did apparently penetrate to the ectopic center, for measurement shows that the periods of interruption are not uniformly exact multiples of the length of the paroxysmal cycle, and consequently that the abnormal rhythm was not merely submerged but was brought temporarily to an end and was reestablished when the interfering rhythm terminated.

We were unable to demonstrate by measurement that the interval separating two successive ventricular extrasystoles occurring during the period immediately preceding the onset or immediately following the termination of a paroxysm was uniformly an exact multiple of the paroxysmal cycle length even when the extrasystoles were occurring regularly. When two paroxysms were separated by a single beat of sinus origin, the interval which separated the last beat of one paroxysm from the first beat of the other was not found to be an exact multiple of the length of the paroxysmal cycle. It would appear, therefore, that the paroxysmal center did not function continuously throughout the period of abnormal heart action and that the extrasystolic arrhythmia occurring between paroxysms cannot be regarded as due to parasystole with exit-block unless it is assumed that the paroxysmal rate was not the full rate of the paroxysmal center.

SUMMARY

There is a type of paroxysmal ventricular tachycardia in which the abnormal mechanism is induced by emotion and exertion. The attacks may be long, but more often short attacks separated by periods of extrasystolic arrhythmia occur in rapid succession. In the majority of the cases there is no other evidence of cardiac disease. Patients with this disorder are usually seriously incapacitated. Small doses of quinidine are often strikingly beneficial but do not always prevent the occurrence of attacks.

In one of the cases studied by the authors a long paroxysm of ventricular tachycardia was frequently interrupted temporarily by short attacks of paroxysmal auricular tachycardia.

REFERENCES

1. Gallavardin, L., and Veil, P.: Deux nouveaux cas de tachycardie en salves chez de jeunes sujets, Arch. d. mal. du coeur **20**: 1, 1927.
2. Gallavardin, L., and Dumas, A.: Contribution a l'étude des tachycardies en salves, Arch. d. mal. du coeur **17**: 87, 1924.
3. Gallavardin, L.: De la tachycardie paroxystique à centre excitable, Arch. d. mal. du coeur **15**: 1, 1922.
4. Idem: Extra-systolie ventriculaire à paroxysmes tachycardiques prolongés, Arch. d. mal. du coeur **15**: 298, 1922.
5. Idem: Extra-systolie auriculaire à paroxysmes tachycardiques, Arch. d. mal. du coeur **15**: 774, 1922.
6. Scott, R. W.: Observations on a Case of Ventricular Tachycardia With Retrograde Conduction, Heart **9**: 297, 1921-1922.
7. Wenckebach, K. F., and Winterberg, H.: Die Unregelmässige Herztätigkeit, 1927, Leipzig, Wilhelm Engelmann.

8. Anderson, M. C.: Paroxysmal Ventricular Tachycardia, Am. J. M. Sc. **181**: 369, 1931.
9. Gilchrist, A. R.: Paroxysmal Ventricular Tachycardia, AM. HEART J. **1**: 546, 1926.
10. Allan, G. A.: Case of Paroxysmal Tachycardia of Ventricular Origin With Stokes-Adams Syndrome, Exhibiting Retrograde Conduction With Partial Heart-Block, Glasgow M. J. **5**: 440, 1926.
11. Hume, W. E.: Observations in Six Cases of Paroxysmal Tachycardia, Quart. J. Med. **11**: 131, 1917-18.
12. Willius, F. A.: Paroxysmal Tachycardia of Ventricular Origin, Boston M. & S. J. **178**: 40, 1918.
13. Levy, A. G.: The Exciting Causes of Ventricular Fibrillation in Animals Under Chloroform Anesthesia, Heart **4**: 319, 1912-13, The Genesis of Ventricular Extrasystoles Under Chloroform With Special Reference to Consecutive Ventricular Fibrillation, Ibid. **5**: 299, 1913-14, Further Remarks on Ventricular Extrasystoles and Fibrillation Under Chloroform, Ibid. **7**: 105, 1918-20.
14. Beattie, J., Brow, G. R., and Long, C. N. H.: Physiological and Anatomical Evidence for the Existence of Nerve Tracts Connecting the Hypothalamus With Spinal Sympathetic Centers, Proc. Roy. Soc., London, Series B. **106**: 253, 1930.

FURTHER OBSERVATIONS ON THE HEART IN OLD AGE. A POSTMORTEM STUDY OF 381 PATIENTS AGED SEVENTY YEARS OR MORE

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IN a previous publication, one of us[2] presented a clinical study of the hearts of 700 aged persons, and brought forth evidence to show that most aged persons, even in the presence of heart disease, possess hearts of unusual quality. The heart that allows life to continue to advanced age is an organ of rare integrity.

Statistical studies have clearly shown that the greatest mortality from heart disease occurs between the fiftieth and the seventieth years of life, and it appears that persons who have survived this period are more likely ultimately to succumb to other diseases, such as carcinoma, pneumonia, or nephritis. It thus seems that nature selectively eliminates the "cardiac group" in the prime of life, and the survivors are largely destined to continue life with relatively adequate cardiovascular systems, awaiting deterioration from other causes.

THE PRESENT STUDY

It seemed desirable to augment the previous study by analysis of the records of necropsy of aged patients, with the idea of obtaining the following information: quantitative data on the incidence and degree of coronary, aortic, and valvular sclerosis; comparative data regarding cardiac weights with reference to hypertension and other factors concerned with cardiac hypertrophy, and the incidence of pathological changes other than arteriosclerosis.

Material.—We studied the postmortem records for a period of ten years, selecting all patients of seventy years of age and older, regardless of the cause of death. We obtained 381 cases among 5,751 postmortem records, an incidence of 6.6 per cent. The age of the patient was the only basis on which selection was made.

In order to show that we appreciate the fact that our material may differ from that in other localities we quote from the previous publication. "It must be acknowledged that the results of critical analysis of this selected material are not entirely comparable to those that might be derived from a similar number of cases, of patients of the same ages as those selected, taken from the general population or from other limited fields of the general population. It must be assumed that the majority of aged patients who seek medical advice at a clinic which is more or less distant from their homes have ailments that may not exist to the same degree and extent among patients in other groups."

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Age.—In order to simplify the presentation of statistical data, the cases were apportioned into age groups of five years, with the exception of those which occurred in the tenth decade of life. Only four patients were ninety years of age or older, and these were considered in one age group. More than half (59.4 per cent) of the patients were between the ages of seventy and seventy-four years (Table I). The incidence naturally diminished as the later age periods were reached. There were sixty patients (15.7 per cent) eighty years of age or older.

Sex.—There was a marked predominance of males (Table I), the incidence being 5 to 1. The high incidence of males was in part influenced, as in the previous study, by a relatively large number of old men suffering from hypertrophy of the prostate gland.

TABLE I

INCIDENCE BY AGE AND SEX

AGE GROUP, YEARS	CASES	PER CENT	MALES		FEMALES	
			CASES	PER CENT	CASES	PER CENT
70 to 74	226	59.4	187	82.7	39	17.3
75 to 79	95	24.9	82	86.3	13	13.7
80 to 84	35	9.2	22	62.9	13	37.1
85 to 89	21	5.5	15	71.4	6	28.6
90 to 99	4	1.0	2	50.0	2	50.0
Total	381	100	308	80.8	73	19.2

Coronary Sclerosis.—Some degree of coronary sclerosis was present in all the cases, although great difference in the degree of involvement was noted. The degree of involvement was graded from 1 to 4, the former indicating little arterial change, whereas the latter denoted very extensive and advanced atherosclerosis. It is interesting to note that in ten cases (2.6 per cent) changes in the coronary arteries were scarcely perceptible (Table II); these cases were in the first age group, seventy to seventy-four years. From the averages in Table II, it is apparent that the coronary arteries of the majority of aged patients (276 cases, 72.5 per cent) reveal moderate to advanced (grades 2 to 4) atherosclerosis. This is a significant fact, and one that finds very definite application in the consideration of aged patients, not only from the standpoint of medical problems but particularly when the question of surgical intervention arises. No definite correlation between the various age groups and the degree of coronary sclerosis was evident in this study.

Aortic Sclerosis.—Fairly definite parallelism between the degree of coronary sclerosis and of aortic sclerosis occurred in this group of patients (Table III), although rather wide variations occurred. Thus,

TABLE II

DEGREE OF CORONARY SCLEROSIS (381 CASES)

AGE GROUP, YEARS	GRADE 1				GRADE 2				GRADE 3				GRADE 4			
	TOTAL CASES	PER CENT	MALES	FEMALES	TOTAL CASES	PER CENT	MALES	FEMALES	TOTAL CASES	PER CENT	MALES	FEMALES	TOTAL CASES	PER CENT	MALES	FEMALES
70 to 74	73	32.3	61	12	94	41.6	74	20	44	19.5	38	6	15	6.6	14	1
75 to 79	24	25.3	20	4	42	44.2	38	4	25	26.3	21	4	4	4.2	3	1
80 to 84	5	14.3	3	2	14	40.0	8	6	11	31.4	8	3	5	14.3	3	2
85 to 89	3	14.3	2	1	9	42.8	7	2	9	42.9	6	3	0	0	0	0
90 to 99	0	0	0	0	1	25.0	0	1	2	50.0	1	1	1	25.0	1	0
Total and percentage	105	27.5	86	19	160	42.0	127	33	91	23.9	74	17	25	6.6	21	4

TABLE III

DEGREE OF AORTIC SCLEROSIS (381 CASES)

AGE GROUP, YEARS	GRADE 1				GRADE 2				GRADE 3				GRADE 4			
	TOTAL CASES	PER CENT	MALES	FEMALES	TOTAL CASES	PER CENT	MALES	FEMALES	TOTAL CASES	PER CENT	MALES	FEMALES	TOTAL CASES	PER CENT	MALES	FEMALES
70 to 74	56	24.8	46	10	103	45.5	90	13	61	27.0	48	13	6	2.7	3	3
75 to 79	17	17.9	16	1	47	49.4	41	6	29	30.6	24	5	2	2.1	1	1
80 to 84	1	2.9	1	0	15	42.8	10	5	18	51.4	10	8	1	2.9	1	0
85 to 89	2	9.6	1	1	5	23.8	4	1	12	57.1	8	4	2	9.5	2	0
90 to 99	0	0	0	0	1	25.0	1	0	2	50.0	1	1	1	25.0	0	1
Total and percentage	76	20.0	64	12	171	44.9	146	25	122	32.0	91	31	12	3.1	7	5

moderate to advanced aortic sclerosis occurred in 305 cases (80 per cent). As in the case of coronary sclerosis, no definite relationship between the various age groups and the degree of aortic sclerosis was observed.

Valvular Sclerosis.—Varying degrees of valvular sclerosis occurred in 353 cases (92.7 per cent). As would be anticipated, the valves of the left side of the heart were involved much more frequently than were those of the right side. The mitral and aortic valves were sclerosed to varying degrees in 304 cases (86.1 per cent), whereas the tricuspid and pulmonic valves were involved in only forty-nine cases (13.9 per cent), a ratio of 6 to 1.

Curiously, the frequency of sclerosis of the mitral valve (157 cases, 44.5 per cent) slightly exceeded that of sclerosis of the aortic valve (147 cases, 41.6 per cent). The degree of sclerosis of the mitral valve was slight (grade 1) in eighty-eight cases (56 per cent); moderate (grade 2) in sixty-four cases (40.8 per cent), and marked (grade 3 to 4) in only five cases (3.2 per cent). The degree of sclerosis of the aortic valve was more marked. The sclerosis was slight (grade 1) in fifty-eight cases (39.5 per cent), moderate (grade 2) in sixty-seven cases (45.6 per cent), and marked (grade 3 to 4) in twenty-two cases (14.9 per cent).

The tricuspid valve was the seat of sclerosis in thirty-two cases (9.1 per cent), whereas the pulmonic valve was involved in only seventeen cases (4.8 per cent). The degree of sclerosis of the tricuspid valve was as follows: slight involvement (grade 1) nineteen cases (59.4 per cent); moderate involvement (grade 2) twelve cases (37.5 per cent); and marked involvement (grade 3 to 4) only one case (3.1 per cent). In the pulmonic valve, the degree of sclerosis was slight (grade 1) in nine cases (52.9 per cent); moderate (grade 2) in seven cases (41.2 per cent); and marked (grade 3) in only one case (5.9 per cent).

No constant correlation between the degree of valvular sclerosis and the various age groups could be determined.

Associated Cardiac Disease Other Than Arteriosclerosis.—We were interested in determining the incidence of associated cardiac disease in this group of aged patients, particularly to ascertain the frequency of lesions acquired in the earlier periods of life that did not materially interfere with cardiac function, and, in spite of their presence, permitted the patient to live to an advanced age.

Associated cardiac disease occurred in sixty-one cases (16.4 per cent). Evidence of healed cardiac infarction was found in fifteen cases; eleven of the patients died of heart failure. Acute cardiac infarction was observed in eleven cases, death in all instances ensuing soon after the onset of the attack. Evidence of old, healed endocarditis was found in fourteen cases; in one case mitral stenosis was well marked, and in three cases marked aortic stenosis with calcification occurred.

Pericarditis was present in twelve cases; chronic adherent pericarditis was found in five, chronic fibrinous pericarditis in three, and acute fibri-

nous pericarditis in four. Acute bacterial endocarditis, an incident in generalized sepsis, occurred in five cases. Only three cases of syphilitic aortitis were observed. In one case, carcinoma had metastasized to the heart.

TABLE IV

SYSTOLIC BLOOD PRESSURE OF 371 PATIENTS SEVENTY YEARS OF AGE OR OLDER

BLOOD PRESSURE, MM. OF MERCURY	AGE GROUP, YEARS										TOTAL	
	70 TO 74		75 TO 79		80 TO 84		85 TO 89		90 TO 99			
	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	CASES	PER CENT
80 to 89	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0	1	0.3
90 to 99	5	100.0	0	0.0	0	0.0	0	0.0	0	0.0	5	1.3
100 to 109	11	73.3	2	13.3	1	6.7	0	0.0	1	6.7	15	4.1
110 to 119	15	51.7	9	31.0	4	13.8	1	3.5	0	0.0	29	7.8
120 to 129	19	59.4	8	25.0	3	9.4	1	3.1	1	3.1	32	8.6
130 to 139	30	56.6	16	30.2	4	7.5	3	5.7	0	0.0	53	14.3
140 to 149	36	69.2	10	19.2	4	7.8	1	1.9	1	1.9	52	14.0
150 to 159	32	61.5	11	21.1	4	7.8	5	9.6	0	0.0	52	14.0
160 to 169	18	47.3	13	34.2	5	13.1	1	2.7	1	2.7	38	10.2
170 to 179	19	63.3	8	26.7	1	3.3	2	6.7	0	0.0	30	8.1
180 to 189	15	65.3	3	13.0	3	13.0	2	8.7	0	0.0	23	6.2
190 to 199	5	45.4	4	36.4	1	9.1	1	9.1	0	0.0	11	2.9
200 to 209	6	46.2	3	23.1	1	7.6	3	23.1	0	0.0	13	3.6
210 to 219	4	50.0	4	50.0	0	0.0	0	0.0	0	0.0	8	2.2
220 to 229	1	20.0	1	20.0	3	60.0	0	0.0	0	0.0	5	1.3
230 to 239	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	1	0.3
240 to 249	2	66.7	1	33.3	0	0.0	0	0.0	0	0.0	3	0.8
Total	218		93		35		21		4		371	100.0
Mean blood pressure	117.3		118.7		119.8		125.0		107.0			
Percentage more than 140 mm.	63.3		62.3		62.8		76.1		50.0			

Blood Pressure.—Records of blood pressure were available for study in 371 cases (97.3 per cent). In numerous cases the average of several readings was accepted, whereas in others only single readings were recorded.

In the previous study, in which readings of blood pressure of 700

aged patients were investigated, it was determined that 74.5 per cent had systolic blood pressure of 140 mm. or more, that 40.3 per cent had diastolic blood pressure of 90 mm. or more, and that 69.6 per cent had pulse pressures of 60 mm. or more. The range of the mean pressure, or the arithmetic average of the systolic and diastolic pressures, was 109 to 127.8 mm. These figures indicated a tendency to readings usually seen in hypertension among older patients.

TABLE V

DIASTOLIC BLOOD PRESSURE OF 371 PATIENTS SEVENTY YEARS OF AGE OR OLDER

BLOOD PRESSURE, MM. OF MERCURY	AGE GROUP, YEARS										TOTAL	
	70 TO 74		75 TO 79		80 TO 84		85 TO 89		90 TO 99			
	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	CASES	PER CENT
40 to 49	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	1	0.3
50 to 59	5	45.5	2	18.2	3	27.2	1	9.1	0	0.0	11	2.9
60 to 69	22	59.5	7	18.9	4	10.8	3	8.1	1	2.7	37	9.9
70 to 79	57	61.3	29	31.2	4	4.3	3	3.2	0	0.0	93	25.1
80 to 89	60	65.3	16	17.4	10	10.8	4	4.3	2	2.2	92	24.8
90 to 99	37	50.7	21	28.8	8	10.9	6	8.2	1	1.4	73	19.7
100 to 109	20	57.1	11	31.4	1	2.9	3	8.6	0	0.0	35	9.4
110 to 119	10	58.8	4	23.5	3	17.7	0	0.0	0	0.0	17	4.6
120 to 129	6	75.0	1	12.5	1	12.5	0	0.0	0	0.0	8	2.2
130 to 139	1	33.3	1	33.3	1	33.3	0	0.0	0	0.0	3	0.8
140 to 149	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	1	0.3
Total	218		93		35		21		4		371	100.0
Mean blood pressure	117.3		118.7		119.8		125.0		107.0			
Percentage more than 90 mm.	33.9		40.8		40.0		47.6		25.0			

In the present study (Table IV), slightly lower averages were obtained, influenced perhaps to some degree by inclusion of patients of a younger age group, seventy to seventy-four years. Two hundred thirty-six patients of the 371 (63.6 per cent) had systolic blood pressure of 140 mm. or more. Of the patients with systolic blood pressure of 140 mm. or more, 196 (83 per cent) were found to be between the ages of seventy and seventy-nine years, inclusive. Thirty patients (13.2 per cent) had systolic blood pressure of 200 mm. or more.

The mean blood pressure for the various age groups can be read on

Tables IV, V and VI. No constant correlation between elevation of systolic and of diastolic blood pressure was apparent. Only 137 patients (36.9 per cent) had diastolic blood pressure of 90 mm. or more. The diastolic blood pressure ranged from 60 to 120 mm. in 219 cases (59 per cent) (Table V). Readings of pulse pressure of 60 mm. or more occur-

TABLE VI

PULSE PRESSURE OF 371 PATIENTS SEVENTY YEARS OF AGE OR OLDER

BLOOD PRESSURE, MM. OF MERCURY	AGE GROUP, YEARS										TOTAL	
	70 TO 74		75 TO 79		80 TO 84		85 TO 89		90 TO 99			
	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	CASES	PER CENT
10 to 19	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.3
20 to 29	2	50.0	1	25.0	0	0.0	1	25.0	0	0.0	4	1.0
30 to 39	12	66.7	4	22.2	2	11.1	0	0.0	0	0.0	18	4.8
40 to 49	30	62.5	11	22.9	4	8.3	1	2.1	2	4.2	48	12.9
50 to 59	45	58.4	18	23.4	9	11.7	4	5.2	1	1.3	77	20.7
60 to 69	42	59.1	18	25.4	8	11.3	3	4.2	0	0.0	71	19.4
70 to 79	32	64.0	13	26.0	4	8.0	1	2.0	0	0.0	50	13.4
80 to 89	25	56.8	10	22.7	2	4.6	6	13.6	1	2.3	44	11.8
90 to 99	18	75.0	5	20.8	1	4.2	0	0.0	0	0.0	24	6.5
100 to 109	7	41.2	5	29.4	2	11.8	3	17.6	0	0.0	17	4.6
110 to 119	2	15.4	7	53.8	3	23.1	1	7.7	0	0.0	13	3.5
120 to 129	1	50.0	1	50.0	0	0.0	0	0.0	0	0.0	2	0.5
130 to 139	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.3
140 to 149	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
150 to 159	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	1	0.3
Total	218		93		35		21		4		371	100.0
Mean blood pressure	117.3		118.7		119.8		125.0		107.0			
Percentage more than 60 mm.	58.7		63.4		57.1		71.4		25.0			

red in 223 cases (60.1 per cent). In the majority of the cases (316, —— 84.6 per cent) the pulse pressure ranged between 40 to 100 mm. (Table VI).

Low blood pressure occurred infrequently. Readings of systolic blood pressure of less than 120 mm. were recorded in only fifty cases (13.4 per cent), and readings of diastolic blood pressure below 70 mm. were found

in forty-nine cases (13.2 per cent). Studies of blood pressure in this series of aged patients, like those in the previously reported series, clearly indicate the tendency for hypertensive readings to occur.

Weights of the Hearts.—The weights of the hearts in 376 cases (98.5 per cent) were suitable for study. The normal cardiac weight for the individual patient was estimated, utilizing the height-body-weight method of Smith. In any case in which marked loss of body weight had occurred prior to death, as in cachexia of carcinoma, the normal weight for that patient was utilized. We are aware that in the presence of marked loss of body weight some loss in cardiac weight occurs, and that this loss is in no way proportionate to the loss in body weight, but it is impossible to ascribe accurate quantitative values to the loss of cardiac weight. Thus, some degree of error enters into our computations which, however, is probably constant throughout the series.

TABLE VII

ANALYSIS OF WEIGHTS OF HEARTS IN 376 CASES

PERCENTAGE INCREASE OF WEIGHT OVER ESTIMATED NORMAL	RANGE OF INCREASE OVER ESTIMATED NORMAL, GM.	CASES	PER CENT
0	0	108	28.7
3 to 9	8 to 34	52	13.8
10 to 19	27 to 78	66	17.6
20 to 29	57 to 185	56	14.9
30 to 39	77 to 143	24	6.4
40 to 49	104 to 188	23	6.1
50 to 59	96 to 238	18	4.8
60 to 69	157 to 250	11	2.9
70 to 79	198 to 331	10	2.7
80 to 89	251 to 305	2	0.5
90 to 99	227 to 278	3	0.8
100 to 109	379 to 384	2	0.5
110 to 119	407	1	0.3

It is interesting to note that 268 aged persons (71.3 per cent) concerned in this study had varying degrees of cardiac hypertrophy (Table VII). However, if we exclude slight increases in cardiac weight, that is, increases of 9 per cent or less, we still record 216 cases (57.5 per cent), or approximately two-thirds of the series. Cardiac hypertrophy was marked in a fourth of the cases; the estimated increase in cardiac weight exceeded 50 per cent in forty-seven cases (12.5 per cent).

The excess cardiac weights were all readily explained by the presence

of such factors as hypertension, aortic stenosis, adherent pericarditis, healed cardiac infarction, and so forth.

No correlation between cardiac weights and the various age groups as employed in this study could be made (Table VIII). Patients with marked cardiac hypertrophy were irregularly interspersed among all age groups. Likewise, there were no striking differences in cardiac weights of the two sexes.

TABLE VIII

WEIGHTS OF HEARTS ACCORDING TO AGE GROUPS

AGE GROUP, YEARS	TOTAL CASES	CARDIAC HYPERTROPHY					
		CASES	PER CENT	PERCENTAGE INCREASE OF WEIGHT OVER ESTIMATED NORMAL	RANGE OF INCREASE OVER ESTIMATED NORMAL, GM.	HEARTS OF NORMAL WEIGHT	PERCENTAGE OF HEARTS OF NORMAL WEIGHT
70 to 74	224	160	71.4	3 to 102	8 to 379	64	28.6
75 to 79	94	63	67.0	3 to 110	10 to 407	31	33.0
80 to 84	34	28	82.3	3 to 68	12 to 185	6	17.7
85 to 89	21	14	66.7	11 to 59	34 to 205	7	33.3
90 to 99	3	3	100.0	28 to 70	78 to 263	0	0.0

In 175 cases, the clinical history and examination, as well as necropsy, failed to reveal findings pertinent to the production of cardiac hypertrophy. In eighty-eight of these cases (50.2 per cent), the actual and the estimated cardiac weights were in perfect agreement (Table IX).

TABLE IX

CARDIAC WEIGHTS IN CASES IN WHICH NO APPARENT CAUSE FOR HYPERTROPHY WAS DETERMINED (175 CASES)

PERCENTAGE INCREASE OF WEIGHT OVER ESTIMATED NORMAL	RANGE OF WEIGHT OVER ESTIMATED NORMAL, GM.	CASES	PER CENT
0	0	88	50.2
2 to 9	8 to 34	33	18.8
10 to 19	33 to 78	29	16.6
20 to 29	57 to 97	17	9.8
30 to 39	70 to 126	4	2.3
50 to 59	136 to 185	4	2.3

However, in fifty-four cases (31 per cent) the actual weights of the hearts exceeded the estimated normal from 10 to 55 per cent. The most probable explanation of the cardiac hypertrophy in these cases exists in the presence of previous hypertension, which disappeared at the close of the patient's life. There is little doubt that hypertension may spon-

taneously vanish, frequently leaving a hypertrophied heart as a relic of its former existence. This study and the former study of Smith do not indicate that there is increase in the weight of the heart in old age, except such as occurs in the presence of disease.

Causes of Death.—Analysis of the causes of death in this series clearly illustrates the character of the material, and indicates that the cases represent a typical group of aged patients.

Carcinoma led the death list with ninety-three cases, and pneumonia was next with sixty-nine cases. Pyelonephritis occurred in forty-nine cases, whereas death from heart disease occurred in forty-eight cases. The deaths from cardiac disease will be analyzed more fully.

Uremia and sepsis occurred in nineteen cases, respectively; death due to trauma and to pulmonary embolism in seventeen cases; cerebral hemorrhage in thirteen cases; peritonitis in eleven cases; arteriosclerosis in eight cases; pernicious anemia in four cases; lymphatic leucemia in three cases; ulcerative colitis and sarcoma in two cases, respectively. The following diseases were represented by one case each: diabetes mellitus, adenomatous goiter with hyperthyroidism, hepatic cirrhosis, ruptured thoracic aneurysm, intestinal obstruction, Hodgkin's disease, and tuberculosis.

In the forty-eight cases in which death was attributable to the heart, hypertensive heart disease was present in fourteen cases, cardiac failure consequent to healed cardiac infarction in eleven cases, acute cardiac infarction in eleven cases, coronary sclerosis with angina pectoris in seven cases, aortic stenosis in three cases, syphilitic aortitis in one case, and chronic adherent pericarditis in one case.

COMMENT AND SUMMARY

As in the previous publication[2] on the heart of aged persons, this study likewise leads to the conclusion that the hearts of persons who live to old age, in the majority of cases, are of remarkable quality. This finds confirmation in the fact that only forty-eight patients (12.6 per cent) died of heart disease.

This study of the heart comprised 381 patients ranging in age from seventy to ninety-nine years who came to necropsy. Fifty-nine and four-tenths per cent of the patients were between the ages of seventy and seventy-four years, whereas 15.7 per cent were eighty years or older. The ratio by sexes was five men to one woman. Varying degrees of coronary sclerosis occurred in all cases, but the involvement was moderate to advanced in 72.5 per cent of them. Likewise, aortic sclerosis was a constant finding, but existed in from moderate to marked degree in 80 per cent of the cases. Sclerosis of the valves occurred in 92.7 per cent of the cases. Cardiac disease, other than arteriosclerosis, was present in 16.4 per cent of the cases. The readings of blood pressure in 371 cases

indicated a tendency to hypertension. The causes of death in this group of aged patients were diverse. Only 12.6 per cent died of heart disease. This clearly shows the suitability of the material for a study of this nature.

REFERENCES

1. Smith, H. L.: The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, AM. HEART J. **4**: 79, 1928.
2. Willius, F. A.: The Heart in Old Age: a Study of 700 Patients Seventy-Five Years of Age and Older, Am. J. M. Sc. **182**: 1, 1931.

RHEUMATIC HEART DISEASE

II. Incidence and Distribution of the Age of Death*

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THE rôle of rheumatic heart disease in the causation of death was discussed in a previous communication.[1] The absolute frequency of rheumatic heart disease was estimated, and an attempt made to differentiate between the frequency of death from rheumatic heart disease, the frequency of death in which rheumatic heart disease is a contributing factor, and of death in which rheumatic heart disease is present as a non-contributing and incidental finding.

Two sets of data are essential to a study of the natural history of rheumatic heart disease: the age distribution and incidence of (a) the first infection, (b) the death of the patients. The determination of the occurrence of the first rheumatic infection, particularly of the heart, is difficult. The distribution of the age of death, however, can be determined accurately, and this knowledge is pertinent to clinical and public health problems. The present discussion is therefore concerned with that phase of the subject.

Distribution of the Age of Death in Rheumatic Heart Disease

Fig. 1 shows the age distribution in 161 of the total 164 instances of death caused directly by rheumatic heart disease and occurring in a series of 5215 consecutive necropsies performed in the Boston City Hospital between the years 1905 and 1929, inclusive. But few deaths occurred in the first decade. The death rate was distributed mainly over the second to the seventh decades. The largest number of deaths occurred in the fourth and fifth decades; but as many as 37 cases, or 23 per cent, of the total number of deaths occurred in the sixth and seventh decades. In the third decade there was a comparative but perhaps not significant decrease. This fact, that not infrequently rheumatic heart disease may be responsible for death as late as the sixth and seventh decades of life, is often not appreciated in clinical medicine.

The age of death in patients dying from rheumatic heart disease was studied in 68 additional cases in which necropsy was not performed. The diagnosis in this group of cases was based on clinical and laboratory findings. The patients were observed in the Boston City Hospital during the years 1920 to 1929. The distribution of the age of death in this group is shown in Fig. 2, and the curve is not significantly different from that of the 161 necropsied cases. These 68 cases, however, cannot be considered as representative as the necropsy series, for

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undoubtedly some cases of death from rheumatic heart disease are unrecognized in the absence of postmortem studies. Fig. 3 represents the two groups combined. The combined group, comprising 229 cases, is large enough to permit certain general conclusions concerning the distribution of the age of death in rheumatic heart disease.

Willius[2] reported the age distribution of death in 160 cases without necropsy examination, and Coombs[3] in 98 cases with necropsy. As

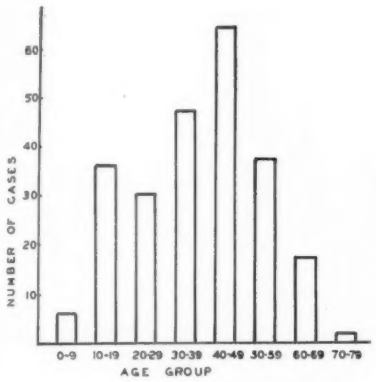

Fig. 1.

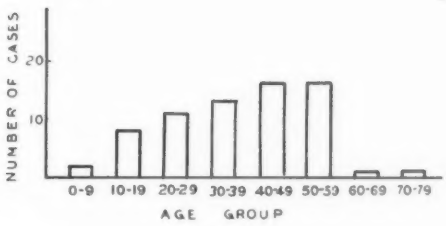

Fig. 2.

Fig. 1.—Age distribution of 161 deaths caused directly by rheumatic heart disease.

Fig. 2.—Age distribution of 68 additional cases of death from rheumatic heart disease in which necropsy was not performed.

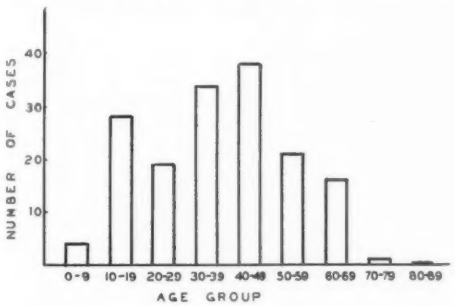

Fig. 3.—Age distribution of 161 autopsied cases of death caused directly by rheumatic heart disease and of 68 additional cases of death in which autopsy was not performed.

these authors apparently did not determine whether or not death in the respective groups was directly due to rheumatic heart disease, their figures are not comparable to those of Fig. 3.

THE AGE OF DEATH IN RHEUMATIC HEART DISEASE COMPLICATED BY SUBACUTE BACTERIAL ENDOCARDITIS AND ACUTE MALIGNANT ENDOCARDITIS

A discussion of the incidence of the age distribution of death due to rheumatic heart disease should include those cases which are complicated by subacute bacterial endocarditis and acute bacterial endocarditis.

These may be regarded as complications which ordinarily occur on the basis of an old rheumatic infection of the heart. Fig. 4 shows the age variation in the group of deaths from subacute bacterial endocarditis. This group comprises 47 cases, 35 of which gave morphological or clinical and morphological evidence of a rheumatic basis. The remaining 12 cases may also have occurred on a basis of rheumatic heart disease, but this was not noted in the postmortem records. In 6 of these cases

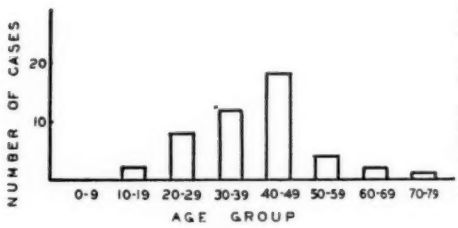

Fig. 4.

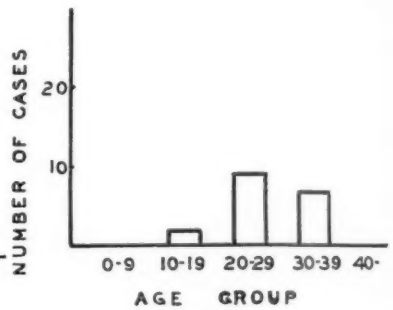

Fig. 5.

Fig. 4.—Age distribution of 47 deaths caused by subacute bacterial endocarditis.
Fig. 5.—Age distribution of 18 deaths caused by primary malignant endocarditis.

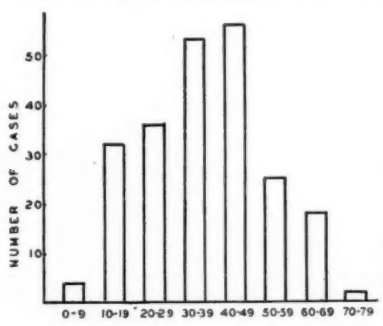

Fig. 6.

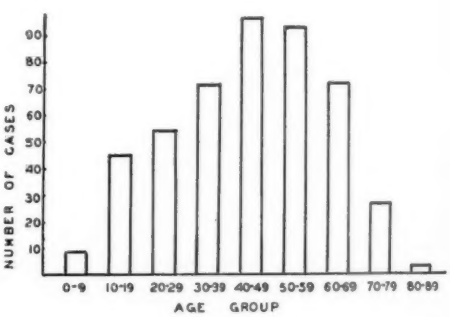

Fig. 7.

Fig. 6.—Age distribution of 226 deaths caused by rheumatic heart disease and by rheumatic heart disease combined with subacute and acute bacterial endocarditis.
Fig. 7.—Age distribution of all 467 cases in which rheumatic heart disease was present as a contributing or noncontributing factor to death.

a history of rheumatic pains and fever was obtained. Subacute bacterial endocarditis occurred at all ages from fifteen to seventy-five years. A relatively large number of cases (40 out of 47) occurred before the age of fifty years. This is somewhat in contrast to the small group of cases with acute malignant endocarditis (Fig. 5) in which all deaths occurred before the age of forty years.

Fig. 6 represents the age distribution in the group of deaths from rheumatic heart disease and rheumatic heart disease combined with subacute and acute bacterial endocarditis. Ages were available in 223 of a total of 232 of these cases. A definite accentuation of the curve occurs again between the ages of thirty and forty-nine years.

Fig. 7 shows the age distribution of all cases in which rheumatic heart disease was present, regardless of whether or not rheumatic heart disease caused death directly, contributed to it, or was present as a mere accidental finding. The character of this distribution curve is essentially the same as that representing the group of cases in which rheumatic heart disease was the cause of death (Fig. 1).

A COMPARISON OF THE AGE DISTRIBUTION IN CASES WITH RHEUMATIC HEART DISEASE WITH THAT OF THE ENTIRE NECROPSY SERIES OF 5215 CONSECUTIVE CASES

Fig. 8 shows the age distribution, expressed in percentage of the total numbers, of the 5060 available cases of the 5215 necropsy series. Curves

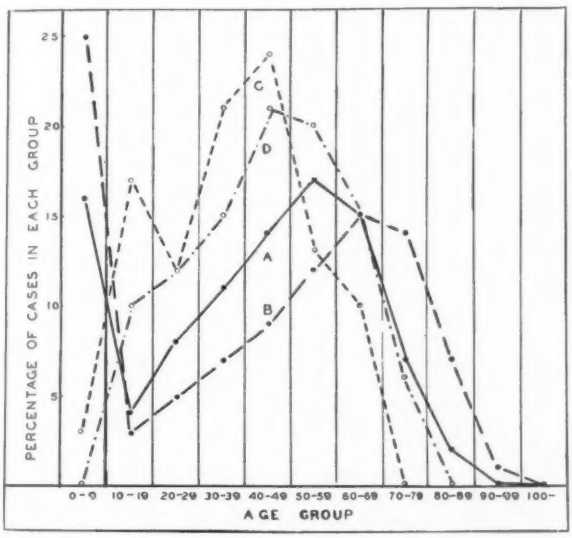

Fig. 8.—*A*, Percentage age distribution of 5060 consecutive deaths, Boston City Hospital (1905-1929). *B*, Percentage age distribution of total deaths in urban population of Massachusetts (average for years 1910, 1916, 1922, 1928). *C*, Percentage age distribution of 161 deaths caused directly by rheumatic heart disease. *D*, Percentage age distribution of all deaths (467) in which rheumatic heart disease was present.

of the age distribution of all cases with rheumatic cardiac manifestations and all cases with rheumatic cardiac death are shown on the same chart for comparison. Fig. 9 represents the same data expressed in absolute numbers. The distribution of the age of death in these 5060 cases taken from the Boston City Hospital and the average distribution reported by the United States Department of Commerce for the urban population of Massachusetts for 1910, 1916, 1922 and 1928, are indicated in Figs. 8 and 9. Although the two curves are not strictly parallel, there is a fair degree of similarity between them. The most outstanding difference is that in the hospital population the deaths predominate between the fourth and seventh decades and are relatively scarce after the seventh decade as com-

pared with the urban population. The probable explanation of this difference lies in the fact that adult and middle aged people with ailments are likely to enter the hospital for relief, while very old people are inclined to stay at home until the time of death. Notwithstanding these differences in the age distribution of the population of the Boston City Hospital and the urban population of Massachusetts, it is felt that with reservations the incidence of rheumatic heart disease in the postmortem series of the Boston City Hospital is roughly applicable to the community as a whole. The application of the age distribution in these 5060 cases to the population at large is further warranted by a comparison of the incidence of a disease such as cancer in the necropsy series with that reported by public health statistics for the entire community. The aver-

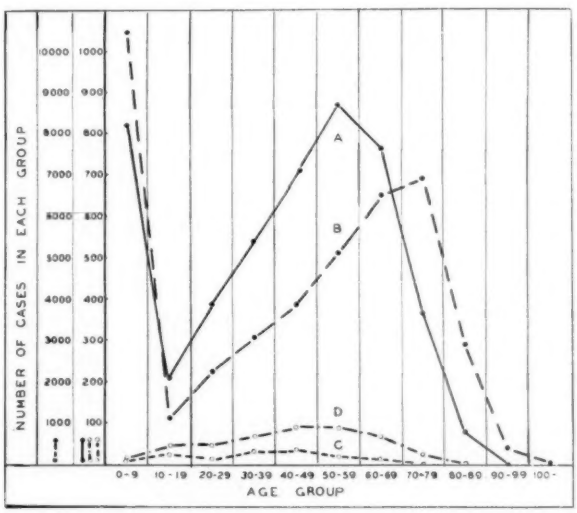

Fig. 9.—*A*, Age distribution of 5060 consecutive deaths, Boston City Hospital (1905-1920). *B*, Age distribution of total deaths in urban population of Massachusetts (average for years 1910, 1916, 1922, 1928). *C*, Age distribution of 161 deaths caused directly by rheumatic heart disease. *D*, Age distribution of all deaths (467) in which rheumatic heart disease was present.

age incidence of cancer in the cases on which necropsy examination was performed was 10.4 per cent between the years 1910 and 1928.[1] The average incidence of cancer in the urban population of Massachusetts was 5.58 per cent in 1910, 7.05 per cent in 1916, 9.12 per cent in 1922, and 10.72 per cent in 1928, with an average of 8.12 per cent for the four years. The gradual increase in the incidence of cancer is attributed to the increasing recognition of the disease rather than to its greater incidence. Hence the figures for the past decade, with an average of between 9 and 10 per cent, are comparable to the average incidence of cancer in 10.4 per cent of the population of the Boston City Hospital.

A comparative examination of the curves (Fig. 9) reveals that approximately 20 per cent of the total necropsied deaths occurring in the

second decade show some earmarks of rheumatic heart disease and that 15 per cent of all deaths in this decade are caused by rheumatic heart disease.

This strikingly high percentage is explained by the relatively small number of deaths from various causes in the second decade of life and the high incidence of the rheumatic infection in the first and second decades. Thus in 114 cases of rheumatic heart deaths (93 with necropsies and 31 without) with a positive rheumatic history, the first symptoms of the infection occurred before the age of twenty-one years in 76 cases (68 per cent). A further contributing factor is the fact that a vast majority of patients with a rheumatic infection occurring in the first decade survive to be exposed to intercurrent disease or die of rheumatic heart disease in the second decade. As indicated before, Fig. 1 shows very few rheumatic deaths in the first decade. The progressive decrease in the percentage of deaths due directly to rheumatic heart disease and the percentage of deaths associated with any degree of rheumatic heart disease is caused mainly by the progressive rise of the incidence of death of the hospital population at large during these decades. There is an apparent rise or stagnation in the seventh decades.

THE PROBABLE DISTRIBUTION OF RHEUMATIC HEART DISEASE AND RHEUMATIC HEART DEATHS IN BOSTON AND ITS VICINITY

Since the age distribution curve of the cases autopsied in the Boston City Hospital is roughly parallel to that of deaths in the population at large, the percentage of deaths from rheumatic heart disease in any given decade should be approximately the same in these two groups. By applying the percentages obtained from the Boston City Hospital figures to the vital and mortality statistics for the State of Massachusetts, one may estimate (1) what number of deaths in the population at large in any given decade may be expected to occur from rheumatic heart disease, and (2) what percentage of the total living population for that decade these probable deaths represent. Table I gives the result of such a calculation. The estimated frequency of fatal rheumatic heart disease varied between 10 to 100 per 100,000 population in 1910 and 10 to 900 in 1920 in various decades.

The frequency of rheumatic heart disease which contributed partially to death, and of that which was present only as an accidental, noncontributing finding at death cannot be estimated for the living population, since the figures representing this type of case cannot be applied statistically from the dead population of the hospital to the living community. In general, however, the statistics suggest that these milder types of rheumatic heart disease must be expected to occur among the living population many times more frequently than that degree of the disease which leads to death.

TABLE I

ESTIMATED FREQUENCY OF RHEUMATIC HEART DISEASE IN THE STATE OF MASSACHUSETTS

DECADE	DEATHS FROM RHEUMATIC HEART DISEASE AND COMPLICATIONS, BOSTON CITY HOSPITAL	TOTAL NECROPSIED DEATHS, BOSTON CITY HOSPITAL	PERCENTAGE OF DEATHS FROM RHEUMATIC HEART DISEASE, BOSTON CITY HOSPITAL	TOTAL DEATHS, STATE OF MASSACHUSETTS, 1920	TOTAL DEATHS, STATE OF MASSACHUSETTS, 1910	ESTIMATED DEATHS FROM RHEUMATIC HEART DISEASE, 1920	ESTIMATED DEATHS FROM RHEUMATIC HEART DISEASE, 1910	TOTAL LIVING POPULATION, STATE OF MASSACHUSETTS, 1920	TOTAL LIVING POPULATION, STATE OF MASSACHUSETTS, 1910	ESTIMATED PERCENTAGE FREQUENCY OF DEATHS CAUSED BY RHEUMATIC HEART DISEASE IN LIVING POPULATION, STATE OF MASSACHUSETTS, 1920	ESTIMATED PERCENTAGE FREQUENCY OF DEATHS CAUSED BY RHEUMATIC HEART DISEASE IN LIVING POPULATION, STATE OF MASSACHUSETTS, 1910
0-9	4	821	.5	12,368	16,524	63	81	745,587	623,732	.008	.013
10-19	32	217	14.7	1,646	1,680	243	248	635,669	581,521	.038	.043
20-29	36	390	9.2	3,282	3,329	303	307	670,967	638,451	.045	.048
30-39	53	542	9.8	3,916	4,102	383	401	608,343	552,030	.062	.073
40-49	56	714	7.8	4,554	4,615	357	362	502,111	421,075	.071	.086
50-59	25	874	2.9	6,154	5,501	176	157	356,776	276,455	.049	.057
60-69	18	758	2.4	7,784	7,168	185	170	207,845	166,241	.089	.103
70-79	2	372	.5	8,049	6,977	43	38	94,095	80,099	.046	.046
80-89	0	83		4,616	3,845			25,507	21,451		
90-99		0		738	603			2,278	1,896		
100-		1		16	23			46	30		
Unknown				9	40			3,132	3,435		

SUMMARY

The incidence and distribution by decades of the age of death of 5060 consecutive necropsy examinations performed in the Boston City Hospital have been analyzed. Deaths from rheumatic heart disease in 229 cases were distributed widely from the second to the fifth decades of life inclusive, the largest number of deaths occurring in the fourth or fifth decades. Of 47 cases in which subacute bacterial endocarditis was superimposed on an old rheumatic heart disease, 40 cases died before the age of fifty years. In all the 19 cases with malignant endocarditis superimposed on rheumatic heart disease death occurred before the age of forty years.

It is to be emphasized that as late as the sixth and seventh decades of life rheumatic heart disease is frequently present in patients with cardiac symptoms and signs. The evidence presented suggests that the age distribution of death of the hospital population studied is roughly parallel to that of the population at large. An estimate of the expected frequency of fatal rheumatic heart disease among the living population of the State of Massachusetts is presented. This estimated frequency of the fatal rheumatic heart disease must, however, represent but a small portion of the total prevalence of rheumatic heart disease in the living population.

REFERENCES

1. Davis, David, and Weiss, Soma: Rheumatic Heart Disease: I. Incidence and Rôle in the Causation of Death. A Study of 5215 Consecutive Necropsies. AM. HEART J. 7: 146, 1931.
2. Willius, F. A.: A Study of the Course of Rheumatic Heart Disease. AM. HEART J. 3: 139, 1927.
3. Coombs, Cary F.: Rheumatic Heart Disease, Bristol, 1924, John Wright & Sons, Ltd.

EXPERIENCES WITH THE DERMATHERM (TYCOS) IN RELATION TO PERIPHERAL VASCULAR DISEASE.

II. STUDY OF ABNORMAL CONDITIONS*

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IN A previous paper we attempted to establish the range of normal variation in skin surface temperatures and published studies on fifty normal medical students.[1] In this paper we shall present the results of our work with the dermatherm in the determination of skin surface temperatures in individuals suffering from various types of peripheral vascular disease. In some instances the cases presented were subjected to only a single series of observations to determine the nature of the skin temperature changes typical of their vascular disturbances. In other cases an attempt was made to follow rather closely the clinical progress of the case as correlated with the changes in skin temperature. In this study, as in our previous work, all determinations were made with the Tycos dermatherm which was developed by the Taylor Instrument Company in collaboration with Dr. W. J. Merle Scott of the University of Rochester Medical School.

For purposes of study we have grouped our cases as follows:

I. General disturbances of peripheral circulation.
   a. Aneurysm of abdominal aorta.
   b. Arteriovenous fistula.
II. Functional disturbances of peripheral circulation.
   a. Raynaud's disease.
III. Ill-defined and unclassified disturbances.
   a. Dermatomyositis.
IV. Diseases of veins.
   a. Varicose ulcer.
   b. Thrombophlebitis.
V. Diseases of arteries.
   a. Arteriosclerosis, diabetic hand.
   b. Arteriosclerosis, diabetic foot.
   c. Diabetic gangrene.
   d. Thromboangiitis obliterans, two cases.

Under general disturbances of the peripheral circulation we consider first a case of aneurysm of the abdominal aorta.

CASE 1.—H. B. was a colored male of forty-eight years, who was admitted to the hospital through the accident ward with a complaint of pain in the back and in the left costovertebral angle. Two years prior to admission he had had a nephrectomy for this same complaint at another hospital. Aneurysm of the aorta was found at this operation, and subsequent examination of the kidney showed it to be normal.

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The patient remained well until three months prior to this admission when he again began to have attacks of sharp pain in the back radiating to the left inguinal region. The attacks were so severe that he had to quit work and go to bed. The pain was usually followed by nausea, gas, sour eructations and occasionally vomiting, and it had been associated with urinary frequency, nocturia, and dysuria. It was made worse by exercising and was partly alleviated by rest.

The patient was a well developed, somewhat undernourished colored male, aged forty-eight years. The eyes reacted to light and accommodation sluggishly. The thorax, heart and lungs were not remarkable. The blood pressure was 150/112 mm. There was a scar in the left lumbar region. There was definite pulsation in the left lumbar region extending to the costovertebral angle. The patient had a right

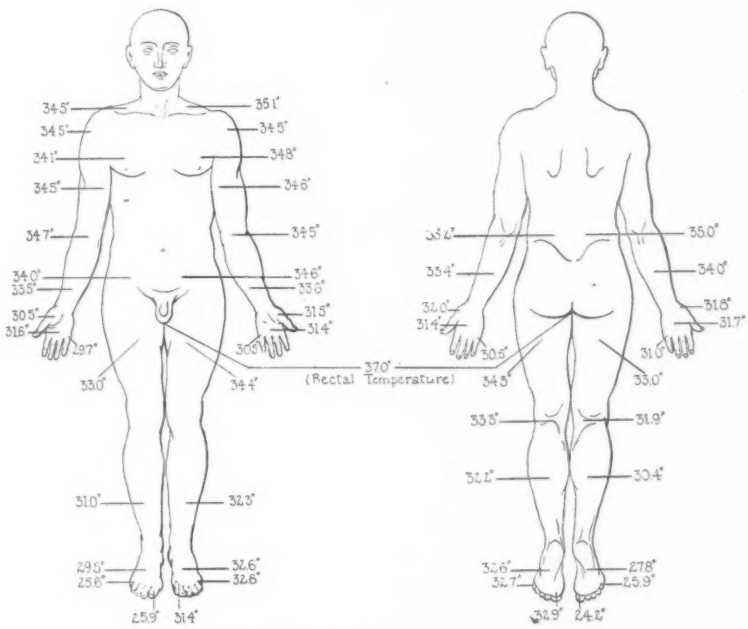

Fig. 1.—Case 1, aneurysm of the abdominal aorta.

scoliosis and tenderness over the lumbar spine. There was apparently no difference in the blood pressure in the extremities. The reflexes were physiological. Repeated urinalyses showed 20 to 30 W.B.C. per high power field; hemoglobin 85 per cent; W.B.C. 11,000; R.B.C. 4,500,000. The blood Wassermann reaction was negative on two occasions. Microscopic precipitation test negative. Blood Urea Nitrogen 16.9 mg. per 100 c.c. and 8 mg. per 100 c.c. Phenolsulphonephthalein exeretion 55 per cent in two hours. X-ray films revealed nothing remarkable in the genitourinary tract. X-ray films of the spine showed the eleventh and twelfth dorsal and the first and second lumbar vertebrae to be partially destroyed. A pneumoperitoneum revealed a mass the size of a grapefruit to the left of the spine, and extending from the level of the transverse process of the ninth dorsal to the lower border of the second lumbar vertebra. Cystoscopy was done and nothing remarkable was found.

Diagnosis: Aneurysm of the aorta.

The patient's hospital course was uneventful and he was discharged. He died at home, approximately one month after leaving the hospital, and an autopsy was not done.

An examination of the dermatherm readings in this case reveals nothing of note other than a more rapid and complete development of the vasomotor gradient from the thigh downward in the right leg. (Fig. 1.) As other pulses were equal and the patient's neurological symptomatology had been practically confined to the left side, it would seem that the increased heat in the left foot was the result of pressure on the lumbar sympathetic chain giving rise to an effect analogous to Horner's syndrome.

A second case within this classification is a case of arteriovenous fistula operated upon by Dr. E. C. Cutler.

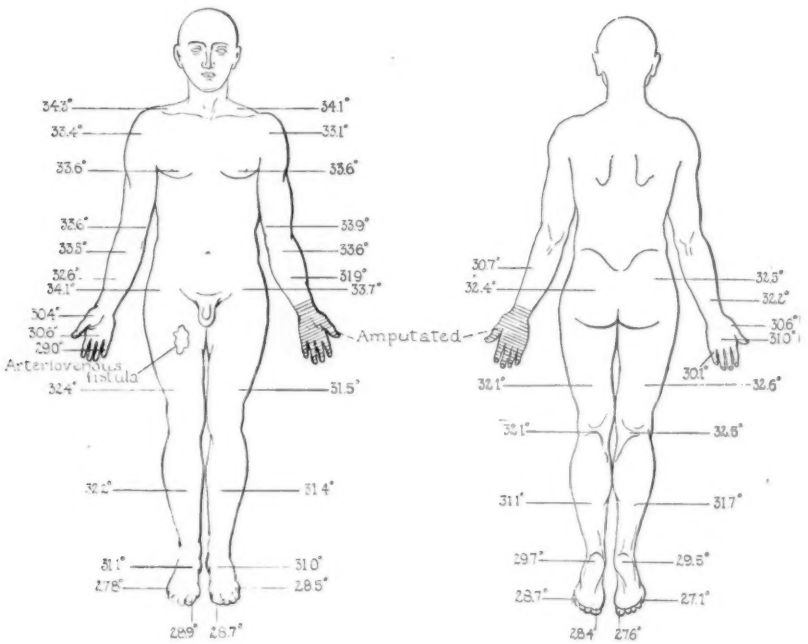

Fig. 2.—Case 2, arteriovenous fistula, preoperative.

CASE 2.—D. H. was a colored male, aged forty-nine years; he was referred to the surgical service from the medical service with the diagnosis of right femoral arteriovenous fistula close to the groin due to a wound by buckshot in 1903. The patient had been studied several times in the hospital for various other complaints. The essential fact in which we are interested is that there was a loud thrill and bruit over a large pulsating aneurysmal dilatation in the right groin. This all disappeared with obliteration of the femoral artery above the pulsation. The pulse rate dropped 40 points with obliteration of the pulsation, and the blood pressure rose about 20 points. With this there was an enlargement of the heart which also became smaller with obliteration of the pulsation. It was thought that this patient had a typical traumatic femoral arteriovenous fistula which was slowly damaging his circulation and which had already caused cardiac hypertrophy, an increased pulse rate, and presumably an increased blood flow with diminished pressure. On the grounds that with increasing age the circulatory apparatus would probably be more seriously em-

barrassed, operation was advised. Dermatherm readings were taken both before and after operation. The readings taken before operation showed a well developed vasomotor gradient in both upper and lower extremities, but no marked disparity between the two sides of the body and no evidence that the lesion in the right groin had appreciably impaired the circulation in the right leg. (Fig. 2.) At operation an extremely small arteriovenous communication with three large traumatic aneurysmal sacs in the major femoral vessel was found. The smallness of the arteriovenous communication probably explained why the patient had sustained so little cardiac damage and why the circulation in the right leg had remained good. The second series of readings taken eight days after operation showed a marked disparity in the temperature of the lower extremities. The right leg was definitely warmer than the left, averaging about 2° C. increase over the left or unaffected side. (Fig. 3.)

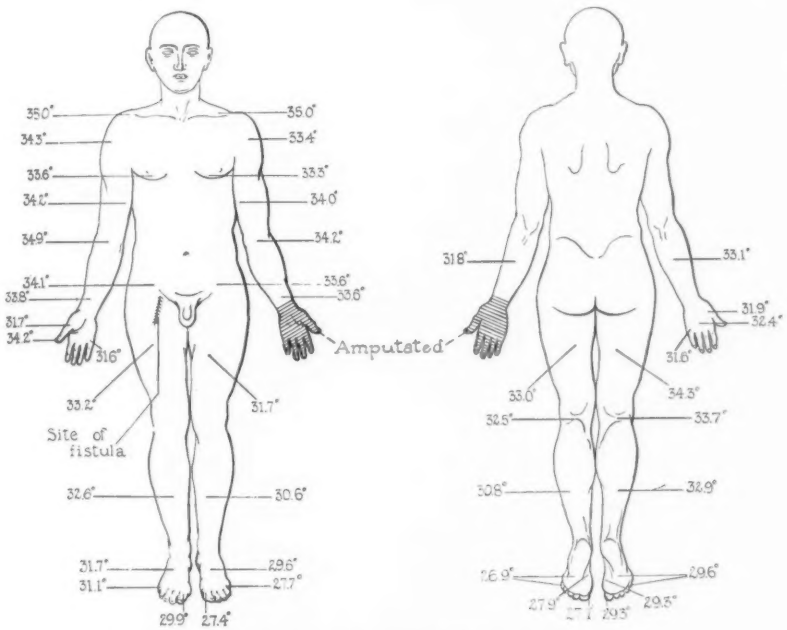

Fig. 3.—Case 2, arteriovenous fistula, postoperative.

The condition was probably not so much the result of improvement of the general circulation, nor change in the mechanical factors influencing the circulation in the right leg, as the natural sequel of a virtual periarterial sympathectomy performed in the course of stripping the adventitia and defining the vessels in the course of the operative repair.

Under the classification of functional disturbances of the peripheral circulation we have a case of Raynaud's disease.

Case 3.—P. M., a white girl of four years, was admitted to the Lakeside Hospital with the complaint that ten days prior to admission she had developed pain in the tips of the fingers, followed shortly afterward by a bluish discoloration. The discoloration and pain had increased and the fingers had felt cold. Four days prior to admission the child was seen at University Hospital at Ann Arbor where a diagnosis of Raynaud's disease was made, and it was advised that sympathectomy be done. The child had been examined at the Elyria Clinic and given intravenous injections of

typhoid vaccine with little improvement. From the Elyria Clinic she was referred to Lakeside Hospital for ganglionectomy. The past history was essentially negative except that the child had always been susceptible to allergic reactions, and had had numerous attacks of hives. The physical examination showed the patient to be a well developed and fairly well nourished white girl of four years, not appearing acutely ill. There was an exfoliative dermatitis over the forehead. There was enlargement of the anterior cervical glands on the left side. The distal ends of the fingers of both hands were cold and showed discoloration extending slightly proximal to the first phalanx. The finger tips were not tender, but the pads showed oval areas which were practically black and appeared to be gangrenous. The radial arteries were readily palpable and the pulse was strong. The middle three toes on both feet were slightly cold, but showed no discoloration unless the child allowed the feet to

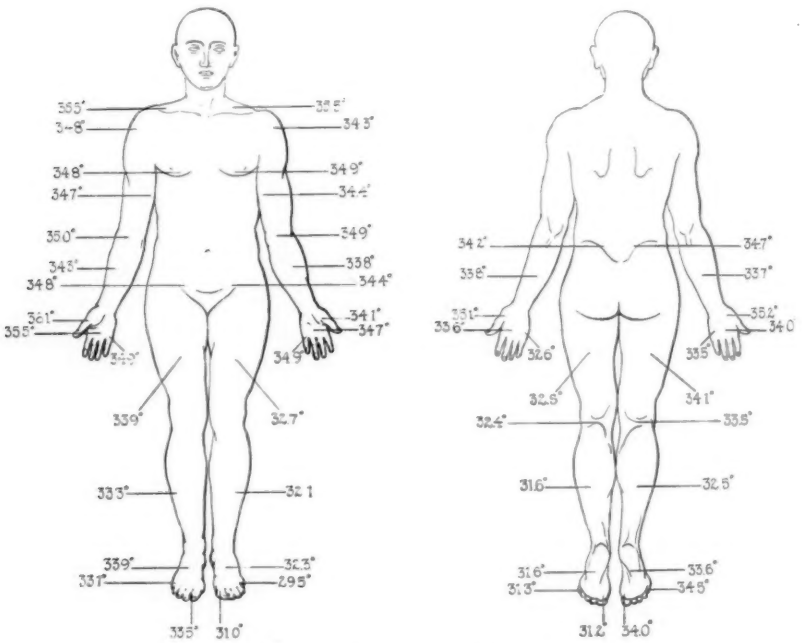

Fig. 4.—Case 3, Raynaud's disease.

hang down, when a slight purplish hue appeared. The dorsalis pedis and posterior tibial arteries were palpable in both feet.

Laboratory findings: Urine negative, W.B.C. 11,100; hemoglobin 80 per cent. The child was carefully studied while in the hospital; dermatherm readings were made of the extremities, and x-ray plates were taken which showed no bony changes of the hands or feet and no evidence of cervical ribs. The family was advised to allow either ganglionectomy or periarterial sympathectomy to be done, but they refused and the child was discharged on release. Dermatherm readings in this case showed an essentially normal development of the vasomotor gradient and no marked disparity between the two sides of the body except the left foot which was 1.5° to 2° colder than the right foot. (Fig. 4.) There was no apparent clinical difference in the severity of the lesions on the two sides.

Case 4.—A rather unusual case which was diagnosed as dermatomyositis was studied. The patient was a white female of five years, who was admitted on the orthopedic service for the treatment of a contracture and flexion deformity of the

right leg. The patient was first seen in the surgical dispensary in December, 1929, with a complaint of pain in the right leg of four or five weeks' duration which had come on following a fall. At the time of the injury the mother had noticed no signs of any serious trouble; however, the child complained of pain in the thigh and leg. The physical examination in the dispensary revealed some induration about the right ankle, with slight limitation of motion at the ankle joint and a ligneous induration of the entire popliteal space, with contracture of the ham-string muscles which limited complete extension by 15 degrees. In January the patient was admitted to the hospital, and at this time the right leg was held in a position of flexion both at the hip and at the knee, and the foot also was dorsiflexed. The subcutaneous tissues and muscles of the entire right extremity felt extremely indurated and were reddened. The knee was flexed about 20 degrees, and the foot was fixed in plantar

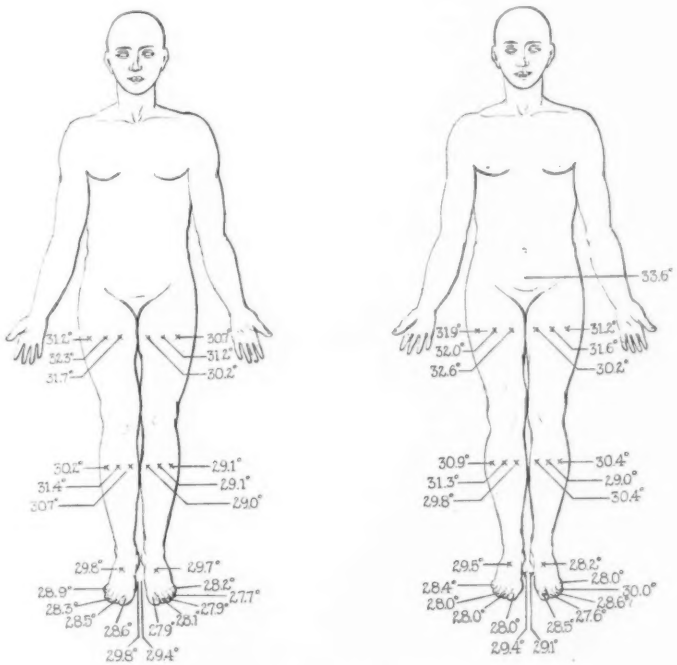

Fig. 5.—Case 4, dermatomyositis.

flexion about 15 degrees beyond a right angle. The diagnosis at that time was ischemic contracture of the lower extremity. A cast was applied and a wedging procedure begun to straighten the leg. The patient was discharged to Rainbow Hospital (convalescent hospital) in February, 1930, where an active pulmonary tuberculosis was discovered. In addition the skin over the right heel broke down due to pressure caused by wedging. An attempt was made to treat the trouble with fibrolysin, but no benefit was obtained. The condition became progressively worse and the child developed exematoid skin lesions over the dorsum of the foot with an increase in the amount of induration in the popliteal space and along the thigh, while the toes became cold and cyanotic. The child returned to Lakeside Hospital in February, 1931, for correction of the deformity.

The physical examination revealed a fairly well developed and well nourished white female child of five years who did not appear acutely ill. The child perspired profusely, the skin being moist at all times. There were several small vesicles on

the face with a few pustules and areas of crusting. The neck showed no thyroid enlargement. There was no lymphadenopathy. The extremities and spine were normal save for the right leg which showed a contracture in the flexed position both at the hip and at the knee. There was a long band of scar tissue extending from the popliteal space to the upper part of the buttock with a similar area on the lateral surface of the right leg. The foot felt mummified; there was a red, indurated crusted lesion on the dorsum and the toes were cold and cyanotic. No pulsation of the dorsalis pedis or posterior tibial arteries could be obtained. There was no motion at the ankle joint, which was fixed in about 30 degrees plantar flexion. The knee was fixed in about 90 degrees flexion with a slight range of motion of about 5 degrees. The right extremity was uniformly smaller than the left. The neurological examination was essentially negative, but reflexes could not be demonstrated be-

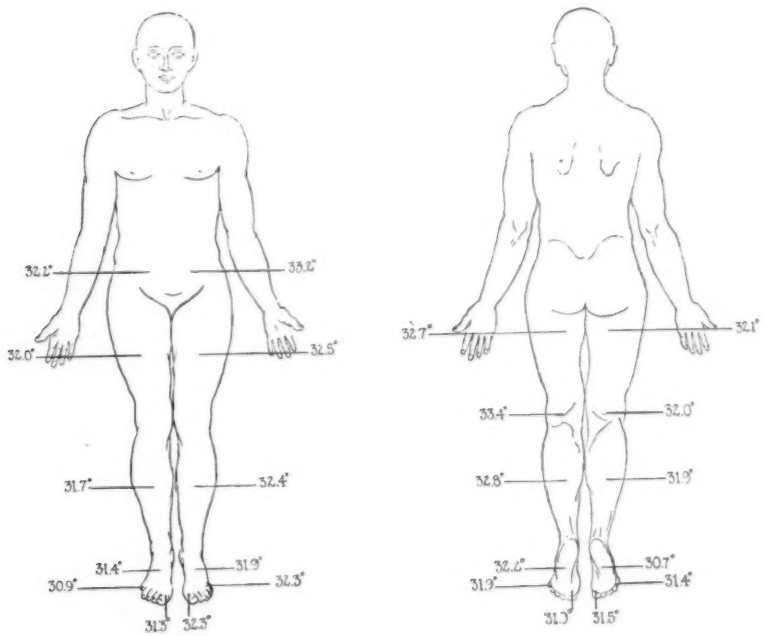

Fig. 6.—Case 5, chronic varicose ulcer of left leg.

cause of fixation of the joints by muscle contracture. There was some shortening of the right leg but the exact amount could not be determined.

The dermatherm readings of the two extremities showed an appreciable difference between the two legs. (Fig. 5.) The vasomotor gradient was very well developed, the distal portion of both extremities being quite low. There was no increase in surface temperature under gas-oxygen-ether, indicating that the impairment of circulation was secondary to a definite anatomical lesion possibly of the nature of a perivascular fibrosis rather than dependent upon vasospasm.

Diseases of veins, such as varicosities with ulceration and thrombophlebitis, were also investigated.

Case 5.—G. B. was a colored female of fifty years, who was admitted to the hospital with the complaint of chronic varicose ulcer of the left leg. The patient had been admitted twice for the same complaint within the preceding two and one-half years, the ulcer having been skin grafted on both occasions. The leg remained

healed until about six months prior to admission when the ulcer reappeared. Local treatment was without avail, and the ulcers increased in size causing considerable disability and discomfort. The patient's left ankle swelled daily and she was forced to keep off her feet. The physical examination was essentially negative except for the left leg which had two large ulcers in the area of the former graft on the anterolateral aspect of the lower one-third of the leg. This area was markedly contracted, its surface was tense, red, and tender, with edema of the leg above and below this area.

X-ray plates of the leg showed marked periostitis of the bone beneath the area of ulceration. The blood Wassermann examination was negative.

Dermatherm readings in this case showed a moderate development of the vasomotor gradient with slightly increased local heat about the left foot and ankle.

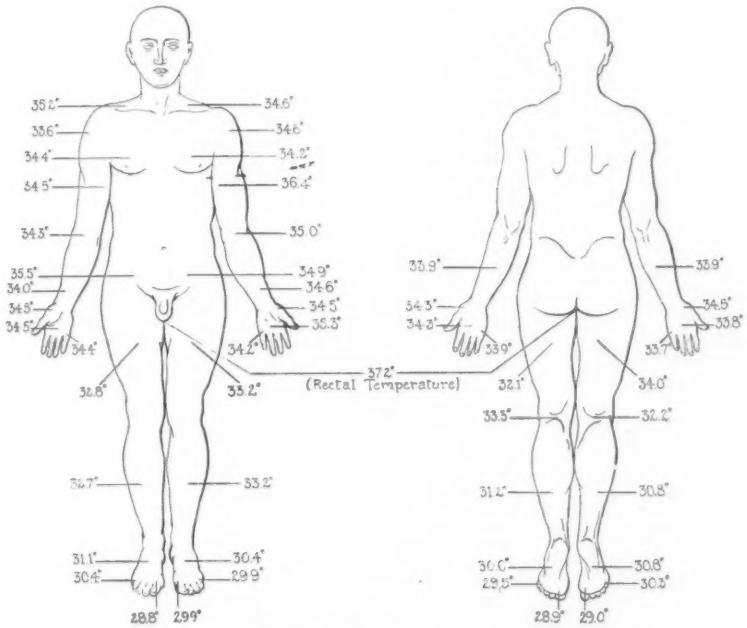

Fig. 7.—Case 6, arterial sclerosis with diabetes mellitus.

(Fig. 6.) These findings are consistent with increased vasodilatation about the inflamed and ulcerated area on the left ankle.

Case 6.—W. S. M. was a white male of sixty-four years, who entered the hospital with a history of striking the top of the left shoulder ten days previously; following this the left arm became swollen and painful. Three days prior to admission a large inflamed area, exquisitely tender, developed on the anterior medial aspect of the left upper arm. The patient had known for nine years that he had glycosuria associated with polyuria, polydipsia and polyphagia. He had been on a limited diet under the care of his family physician for four years. During the past four years he had not adhered to any diet and had lost about 100 pounds, twenty pounds of which had been lost in the preceding three weeks.

The physical examination showed a well developed, emaciated white male of sixty-four years who appeared acutely ill. The eyes showed a moderate arcus senilis. The left side of the neck was swollen, and there was an area of brawny induration extending from the shoulder. There was a prominence over the left shoulder and

marked subcutaneous swelling which obliterated the supraclavicular fossa on the left side and extended down on the anterior medial aspect of the left arm. The left shoulder appeared almost twice the size of the right, and the skin was reddened over the entire area. There was brawny induration present, but no definite fluctuation. The heart and lungs were not remarkable. The blood pressure was 135/115 mm. There was moderate peripheral arteriosclerosis. The abdomen and the genitalia were negative. Laboratory findings: Urine-sugar four plus and a slight trace of albumin. W.B.C. 22,000; blood Wassermann reaction was negative.

After the patient had been in the hospital for several days and had shown considerable clinical improvement, a series of dermatherm readings was taken which showed no marked variation from the normal. (Fig. 7.) The vasomotor gradient was well developed, and there was no marked disparity between the two extremities.

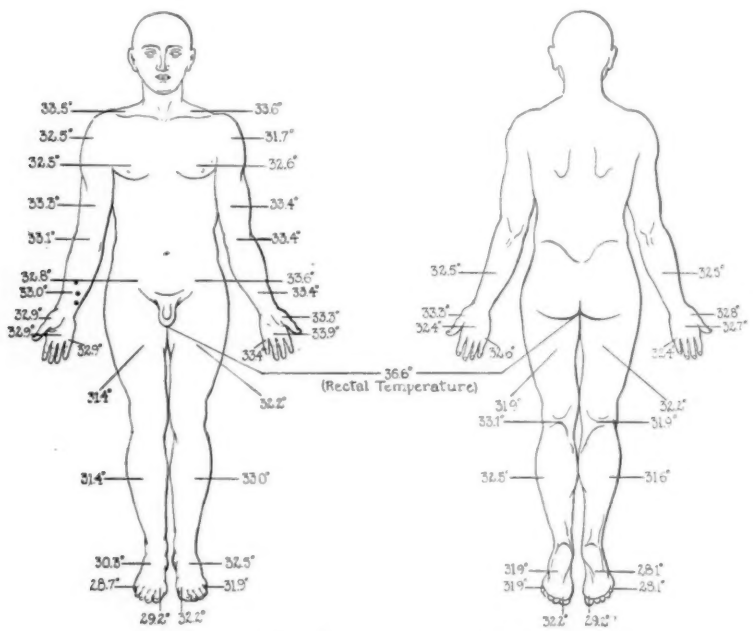

Fig. 8.—Case 7, diabetic gangrene of right foot.

A much more pronounced case of arterial disease was next sought out for study.

Case 7.—C. G. was a white male aged eighty years, who entered the hospital in February, 1931, because of gangrene of the right foot. He had been previously admitted in 1919 with diabetes mellitus and cystitis. A second admission in June, 1930, was because of diabetes mellitus and beginning gangrene of the second and third toes of the right foot. No dietary measures had been followed. Upon discharge the toes were somewhat improved, but two months before the present admission the gangrenous process gradually became worse and the patient was readmitted. He had been treated in the Diabetic Clinic and his last diet was C. 125 P. 85 F. 150 with insulin 20-0-20.

The physical examination revealed a well developed, obese, senile white male of 80 years, lying comfortably in bed. The fundi showed advanced arteriosclerotic changes, and a loud rough systolic murmur was heard over the precordium loudest at the aortic area. The A_2 was greater than P_2 and accentuated. The blood pressure

was 188/98 mm. There was a marked peripheral arteriosclerosis, and a coarse rhythmical intention tremor of the hands. The knee jerks were hypoactive. The right Achilles jerk was absent. The dorsalis pedis and posterior tibial arteries were palpable on both sides. There was a vivid purple color increasing in intensity from the external malleolus of the right foot downward. Although the toes were warm, there was an area of dry gangrene on the first and second toes and varicose veins were present.

In this case the dermatherm readings showed a marked disparity in the circulation present in the lower extremities. (Fig. 8.) The entire right foot, the toes of which were involved in a gangrenous process, was two to three degrees colder than the left foot. Even the upper portions of the extremity were one to two degrees colder than the corresponding areas on the left leg, which showed a well marked vasomotor gradient.

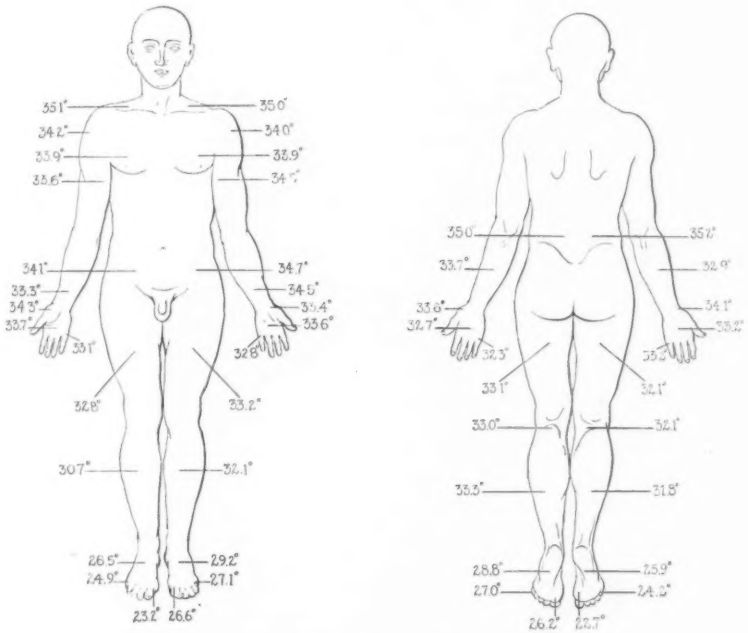

Fig. 9.—Case 8, thromboangiitis obliterans.

Two cases of thromboangiitis obliterans were also studied with the dermatherm, and one of these cases has been followed over a considerable period.

Case 8.—B. K. was a Polish Jew aged forty-one years, who gave a history of first noticing three years before that exercise caused the left leg and foot to become white and initiated cramplike pains in the calf. Stopping exercise or applying heat gave relief. The condition persisted for two winters and then ceased. During the past winter the patient had had the same trouble with the right foot and leg with the addition of a pricking sensation and numbness. Heat did not give relief. There was a past history of typhoid fever in infancy and cystitis and kidney trouble during youth. The family history was negative. The physical examination was essentially negative, except for a coldness of the extremities which was more marked in the right foot and leg. Neither posterior tibial artery was palpable. The left

dorsalis pedis artery was palpable, the right was not. Dermatherm readings in this case showed an extremely well marked progressive drop in surface temperature below the knees, particularly on the right side. (Fig. 9.) There was a variation of 12 degrees between the highest and the lowest surface temperatures recorded which far exceeds the normal variation. The right leg and foot were two to three degrees cooler than the left which also exceeded the normal limits of variation.

CASE 9.—Our other patient, J. G., admitted on the Medical Service August 31, 1930, was a Hungarian male of fifty-five years. The present illness had begun in 1918 when he first froze his feet. In 1919 the patient began to have considerable pain in his feet and noticed that when he walked on the street his toes and feet became very painful. The pain was much worse in the winter than in the summer.

Four weeks prior to his first admission on August 21, 1930, the patient's left great toe became red, swollen and painful. The patient saw a physician who trimmed away part of the nail; after this the patient developed an ulcer. There was a great deal of pain in the left foot, especially across the dorsum.

The physical examination at the time of admission showed a well developed, slender Hungarian male of fifty-five years. The fundi revealed moderate arteriosclerotic changes. Examination of the heart showed a moderate enlargement of the left ventricle with a systolic murmur heard at the apex and over the aortic area. The blood pressure was 210/108 mm. X-ray examination showed an increased prominence of the aortic knob and a left ventricular hypertrophy. The remainder of the physical examination was negative except for the extremities. Both hands and feet showed a patchy cyanosis which was not relieved by elevation. The left great toe was swollen, reddened, the end ulcerated, the nail missing and the end of the bone exposed. There appeared to be a definite line of demarcation as if gangrene had formed. The toe was extremely tender. No dorsalis pedis could be felt in either foot, but both posterior tibials could be palpated. Pea-sized inguinal glands were palpable bilaterally. The reflexes were physiological.

Laboratory examination: urine negative; hemoglobin 110 per cent; red blood count 5,090,000; white blood count 17,000; differential normal; vital capacity 3800 c.c.; phenolsulphonephthalein excretion 40 per cent.

For several days following admission the condition of the left great toe remained virtually unchanged. On the eighth day intravenous injections of killed typhoid bacteria were begun. On the evening of this day the patient began to complain of the right leg being numb below the knee. The leg was bloodless, cold and waxlike. No pain was felt, but sensation was diminished over the lower leg and foot. The impression was that the patient had suffered an arterial thrombosis. A cradle and heat were applied and on the following day the leg had resumed its usual appearance. The patient first received fifteen million typhoid bacilli; one week later twenty million and four days later twenty-five million. At no time did the patient show extreme reaction to the injections. X-ray films in the meantime showed a definite destructive process in the distal digit of the left great toe; a diagnosis of osteomyelitis was made. Periarterial sympathectomy was advised preparatory to amputation of the toe in the hope of obtaining viable amputation flaps. The patient refused treatment, however, and left the hospital September 13, 1930.

The patient was readmitted on the Surgical Service October 22, 1930. The physical findings were essentially those of the previous admission; both hands and feet showed a patchy cyanosis which was not relieved by elevation. The left great toe was swollen and reddened; the nail was missing and the phalangeal bone was exposed. Just proximal to the nail there was a definite line of demarcation suggesting gangrene. The left foot felt warmer than the right, but the pulsation of the dorsalis pedis artery could not be felt on either side. The urine was loaded with red blood cells which cleared completely in one week. The Wassermann reaction was

negative. Blood urea nitrogen 17.5 mg. Blood sugar 132. Phenolsulphonephthalein excretion 65 per cent in two hours.

A fluctuant area of suppuration rapidly developed on the dorsum of the left foot which was incised on the third day, and approximately one ounce of pus was drained. Under treatment with hot sterile dressings and heat lamp the abscess healed rapidly. During this period red blood cells were found in the urine. On the eighth day the histamine dermal test was done on both legs. The wheal and flare were in general more marked on the right leg and were well marked as low down as the ankles on both legs.

A high ligation of the femoral vein and a periarterial sympathectomy of the left femoral artery were then performed under local anesthesia. The condition of the left leg became grossly improved and the toe was much improved. Histamine test

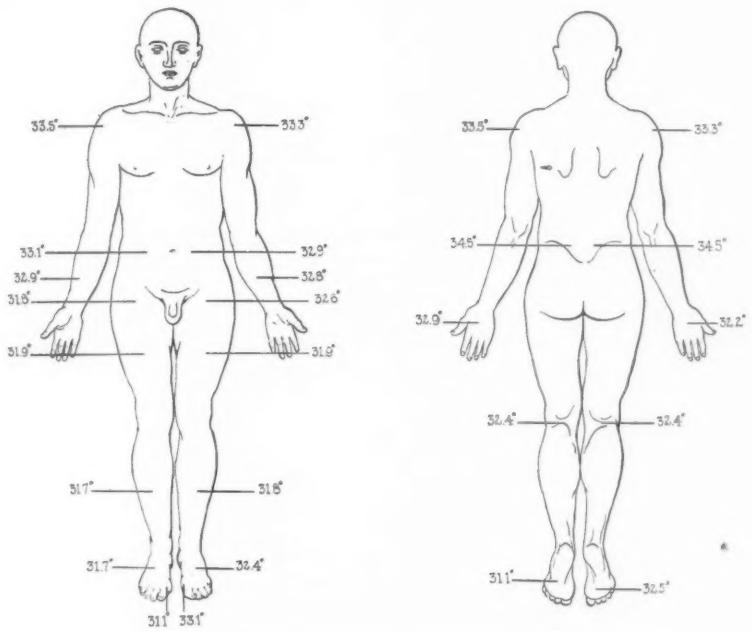

Fig. 10.—Case 9, thromboangiitis obliterans, first admission.

on the twelfth postoperative day showed a flare in seven minutes which was best at ten to twelve minutes. The leg on which the sympathectomy had been performed showed the larger flares, and flaring was well established down to the ankle. The patient was advised to undergo amputation of the left great toe because of infection, but he again refused and was discharged on November 20, 1930.

The first dermatherm studies made in this case at the time of his admission to the Medical Service showed a temperature increase of 0.5 degree in the foot on the affected side. (Fig. 10.) The base of the great toe just proximal to the lesion was one degree Centigrade warmer than the thigh. The vasomotor gradient was not well established in the other extremity. On the second admission to the Surgical Service examination showed the entire left leg to be considerably warmer than the right (0.5 to 1.5 degrees), and the opposite leg showed an increase

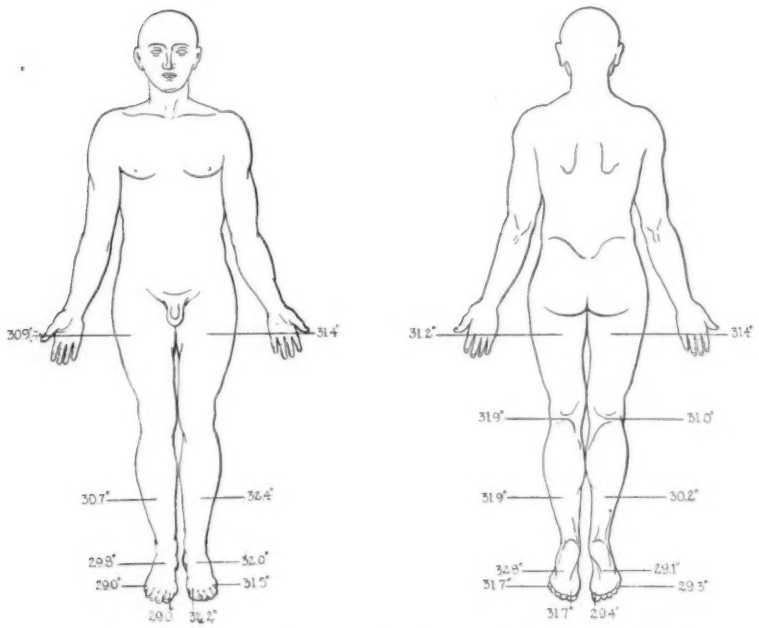

Fig. 11.—Case 9, thromboangiitis obliterans, second admission.

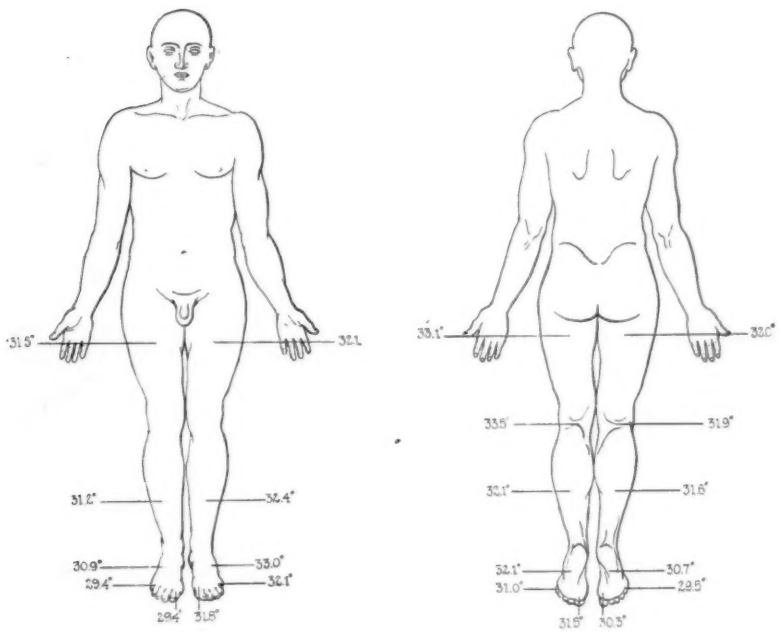

Fig. 12.—Case 9, thromboangiitis obliterans, seventh postoperative day.

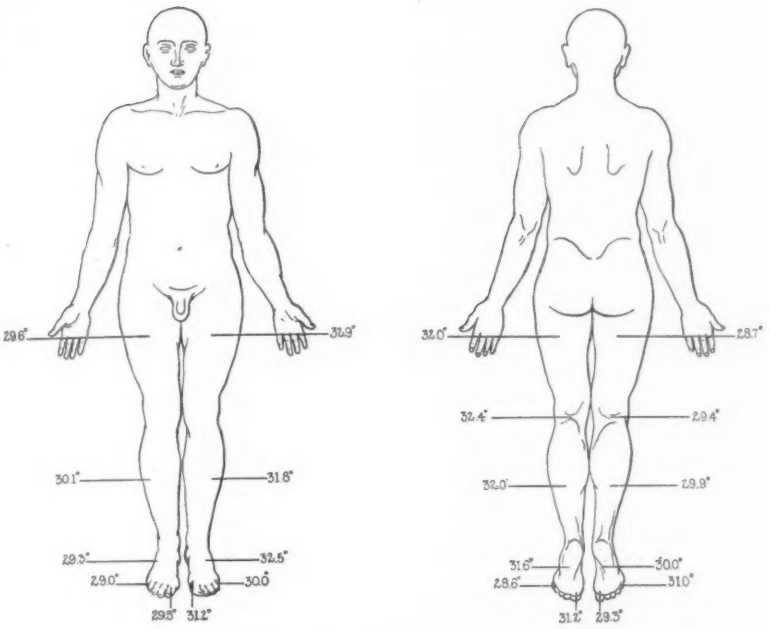

Fig. 13.—Case 9, thromboangiitis obliterans, twelfth postoperative day.

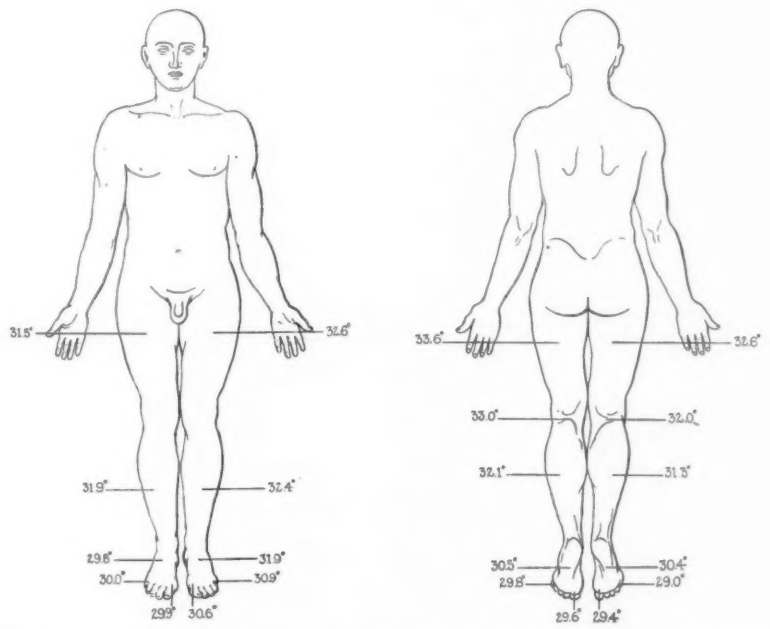

Fig. 14.—Case 9, thromboangiitis obliterans, twentieth postoperative day.

in temperature of 0.5 to 1.0 degree. (Fig. 11.) On the seventh postoperative day this effect on the right left was not observed, and the left leg was definitely warmer than the right. (Fig. 12.) On the twelfth postoperative day the left leg was still definitely warmer than the right, but its temperature was lower than at the time of the previous determination. During this period the local lesion on the great toe had undergone considerable improvement. (Fig. 13.) On the twentieth day the left leg was cooler than the right, but the left foot maintained a higher temperature than the right. (Fig. 14.)

Three features of this study deserve especial attention. The increased temperature in what is presumably the more diseased leg coincident with the development of infection indicated reflex sympathetic vasodilatation. Sympathectomy is evidently accompanied by a transient effect upon the opposite extremity. Finally the falling temperature of the left leg suggests that the effects of sympathectomy are to be only transient and that in refusing operation the patient lost his opportunity to have an amputation before his circulation regressed to its former level.

DISCUSSION

Our previous attempt to establish normal skin temperature averages for a large number of definite points over the body and extremities by studies on fifty normal medical students by the use of the dermatherm (Tycos) resulted in the determination of an average value of 32.5° for the body with a reduction of 1 to 2 degrees for the upper extremities and 2 to 3 degrees for the lower extremities. The vasomotor gradient is most pronounced in the hands and below the knees. The range of temperature variation of 4 to 5 degrees over the body, 4 to 6 degrees over the hands, and 6 to 8 degrees over the feet suggests that no accurate average standard can be set up according to which all patients should be arbitrarily judged. Comparative studies on the same patient to determine the vasomotor gradient, occlusion index, etc., by the use of various means of temporarily or permanently paralyzing the sympathetic supply to the peripheral vessels should prove of great value in estimating the relative part played by vaso-occlusion and vasospasm in the individual case of peripheral vascular disease. It can be stated that in general there is no skin temperature picture which can be considered diagnostic of any given peripheral vascular disease. The principal value of the dermatherm studies is prognostic rather than diagnostic, and the method will be found mainly useful in establishing criteria for the various types of protein shock therapy and the operative procedures upon the sympathetic nervous system which have been attempted for the relief of peripheral vascular disease.

REFERENCE

1. Eddy, H. C., and Taylor, H. P.: Experiences With the Dermatherm (Tycos) in Relation to Peripheral Vascular Disease. I. Normal Studies, Am. Heart J. **6**: 683, 1931.

UNUSUAL DILATATION OF THE LEFT AURICLE*

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DILATATION of one or both auricles to a moderate degree is a common finding in chronic rheumatic carditis, but extreme dilatation of the left auricle is considered rare. The effects of the enlargement of the left auricle on the structures of the mediastinum have been known for a long time and have been repeatedly demonstrated. Among the various complications that may arise, compression of the left bronchus, paralysis of the left recurrent laryngeal nerve, and compression and displacement of the esophagus are the best known.

Many clinicians and roentgenologists, however, are skeptical of the possibility that the left auricle may dilate in a horizontal manner and form a part of the right cardiac border; yet the literature contains a number of such cases. I. Owen and W. J. Fenton[1] in 1901 first described the clinical and pathological features of such extreme enlargement of the left auricle to the right. Since then, other cases have been reported (notably[2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14]). Bordet[15] found the left auricle to the right, beyond the right auricle, in 5 per cent of a large series of cases of mitral stenosis examined by roentgenological methods.

During the past year we have had the opportunity of studying five cases of rheumatic carditis in which dilatation of the left auricle was a prominent feature. The findings in these cases resemble so closely all the reported features of extreme left auricular enlargement that we have deemed them worthy of presentation. In three of these (Figs. 2, 4 and 7), the dilatation was so extreme that the left auricle formed a large part of the right cardiac shadow, while in two others (Figs. 1 and 6), although it did not reach the same degree of dilatation, it produced pressure phenomena sufficient to obstruct the esophagus and caused an erroneous diagnosis of esophageal neoplasm to be made. One of the latter cases is especially interesting and instructive, since in overlooking the possibility of mitral stenosis with left auricular dilatation a gastrostomy was performed in another institution to relieve what was believed to be an inoperable neoplasm.

From this standpoint the lesion described here appears to be more than a mere pathological curiosity, since it serves to illustrate certain dynamic principles which should have a wider appreciation in their relation to cardiac pathology.

The following five cases will serve to exemplify the unusual and severe form of this condition.

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CASE REPORTS

CASE 1.—B. W. A female of fifty years entered the Philadelphia General Hospital in October, 1930, complaining of dyspnea, palpitation, vomiting and inability to swallow solid food. The past history was unimportant except for the occurrence of rheumatic fever at the age of thirteen years. Her present illness started two years ago with dyspnea and at times slight edema of the ankles. For the past two months increasing difficulty in swallowing food had forced her to enter another hospital, where, after an esophageal examination, a diagnosis of malignancy was made, and a gastrostomy performed. She was transferred for radium treatment to this institution where she died on November 20, 1930, of progressive cardiac failure. *Examination:* A female of slender build, emaciated, dyspneic, with slight jaundice and cyanosis. The pulse was completely irregular. The apex was in the sixth interspace in the anterior axillary line but no thrill was felt. No murmurs were heard. The breath sounds were diminished at both bases but no moisture was

Fig. 1.

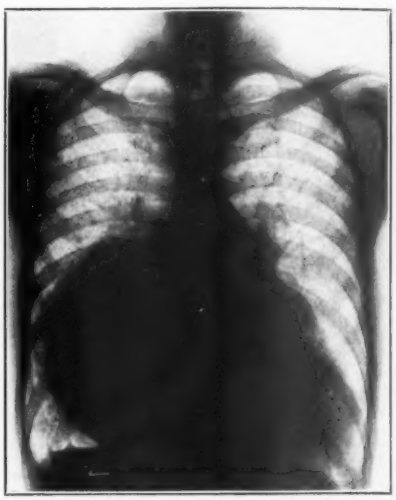

Fig. 2.

Fig. 1.—Case 1. Left oblique view showing obstruction in the esophagus at about the level of the fourth thoracic vertebra, due to large left auricle compressing the esophagus against the spine.

Fig. 2.—Case 2. Enlarged left auricle extending far to the right, over-riding the right auricle and forming the major portion of the right cardiac border. Note elevation of the bronchi and great density on right side due to superimposed left auricle.

present. The liver was enlarged and the spleen could be easily palpated. There was a distinct fluid wave in the abdomen. Electrocardiogram showed auricular fibrillation. *X-ray Examination:* The heart was much enlarged in both directions, the upper left border being broadened, and the pulmonary artery together with the conus were unusually prominent. The angle of the bifurcation of the trachea was widened. Fluoroscopically, the pulsations on the left border of the heart were marked, with feeble pulsations on the right. In the right oblique position the retrocardiac space was entirely filled by the enlarged left auricle. There was a definite obstruction to the flow of barium in the esophagus at the level of the sixth thoracic vertebra (Fig. 1). Above the point of obstruction the esophagus was dilated, while below it the esophagus was displaced posteriorly and the barium passed in a very narrow stream. *Autopsy:* A poorly nourished white female, weighing ninety-four pounds. The abdomen contained 800 c.c. of yellow fluid, and the liver was enlarged and chronically congested. The spleen was enlarged with a greatly thickened capsule.

The lungs showed chronic pleuritic adhesions and scattered areas of consolidation. The heart weighed 390 gm. The valves were all normal except the mitral, which was thickened and contracted, so that it was represented by a mere slit. The auricles were both distended, but the left was twice the size of the right with a thickened endocardium and a thin, transparent epicardium. No adhesions were present. At the junction of the middle and lower third the esophagus was flattened and compressed; the depression made by the left auricle which compressed it against the spine was easily seen. The esophagus showed no evidence of any gross lesion.

CASE 2.—A. W. A male of thirty-three years entered the Philadelphia General Hospital on February 10, 1931, complaining of recurring colds, weakness, cough and loss of weight. He had had a severe rheumatic fever at the age of nine years and was well thereafter except for frequent sore throats until February, 1931, when following tonsillectomy he noticed some palpitation. *Examination:* Except for an appearance of chronic illness he seemed quite comfortable. The important findings

Fig. 3.

Fig. 4.

Fig. 3.—Case 2. Lateral view showing left auricle extending backward and right ventricle in contact with sternum in front.
Fig. 4.—Case 3. Marked dilatation of the left auricle extending to the right and forming the major portion of the right cardiac border. Left ventricle enlarged and a prominent conus on the upper left border.

in his chest were a diminished expansion at the right base with an impaired percussion note over an area corresponding to the right middle lobe in the axilla. Over this area the breath sounds were faint. The heart was enormously enlarged with the apex in the sixth interspace at the anterior axillary line. To the right of the sternum there was dullness in the third and fourth interspaces extending an inch and a half and merging with the liver dullness at the midaxillary line. A diastolic thrill was felt inside the nipple on the left and as far as the midsternum toward the right. A loud systolic murmur was heard all over the precordia, maximum at the apex and heard well to the right of the sternum. A short diastolic murmur was heard inside the left nipple. The pulse was completely irregular. There was no evidence of congestive heart failure. The electrocardiogram showed auricular fibrillation. *X-ray Examination:* The heart was greatly enlarged but markedly so to the right (Fig. 2). The conus of the right ventricle was very prominent. The shadow to the right showed no pulsations and was denser than that on the left side.

The less dense right auricle could be seen to the inner side of the right border of the heart. The tracheal bifurcation was widened. In the right oblique the retrocardiac space was entirely obliterated by the left auricle and the barium filled esophagus was displaced posteriorly and to the right (Fig. 3). *Further History:* Marked improvement followed rest and digitalis therapy. He was discharged in March and returned to his clerical duties. He has continued to work and comes under occasional observation with only slight evidence of breathlessness. *Diagnosis:* Rheumatic heart disease; mitral stenosis; extreme dilatation of left auricle; auricular fibrillation.

CASE 3.—J. B. A young male of nineteen years entered Philadelphia General Hospital in June, 1930, complaining of dull aching pain over his heart and in the right chest anteriorly. At the age of ten he was ill with a severe attack of rheumatic fever, and this was followed by several minor attacks. For the past year he has had epigastric pain radiating to the right shoulder with cough and dyspnea on

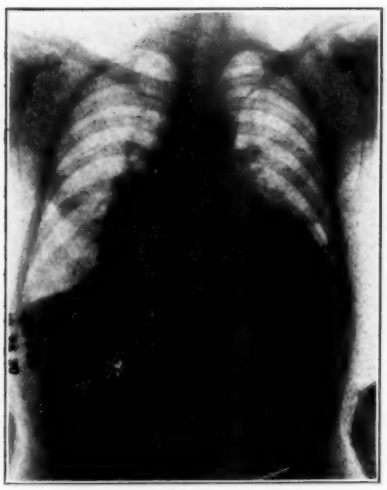

Fig. 5.

Fig. 6.

Fig. 5.—Case 4. Left ventricular hypertrophy with moderate extension of the left auricle to the right which is causing pressure on the esophagus posteriorly.
Fig. 6.—Case 4. Impression of the left auricle on the esophagus with obstruction at its lower portion.

exertion. *Examination:* He was a well-developed young man not acutely ill. His heart was greatly enlarged to both the right and the left, the apex being in the sixth interspace 3 cm. outside the nipple. There was definite impairment to percussion to the right of the sternum in the second, third and fourth interspaces. There was a slight but definite bulging in the third and fourth right interspaces in the axilla with a palpable pulsation. A diastolic thrill was felt inside the nipple. A rough systolic murmur was heard all over the precordia and to the right of the sternum. A short, rough diastolic murmur was localized inside the nipple. The pulse was completely irregular. The liver was barely palpable but no other signs of congestive failure were present. The right lower chest showed markedly diminished expansion with faint breath sounds. Electrocardiogram showed auricular fibrillation. *Bronchoscopic Examination:* The right main stem bronchus was almost completely closed below the bifurcation, due evidently to extrinsic pressure. *X-ray Examination:* The heart showed remarkable enlargement (Fig. 4). There was marked density over the right side of the heart compared with the left, and the

less dense right auricle could be seen to the inner side of the more dense left auricle. There was marked pulsation on the left border of the heart but none on the right. In the right oblique the retrocardiac space was obliterated by the left auricle. Barium in the esophagus showed marked delay at the lower third which was displaced to the right. The tracheal bifurcation was widened, and the pulmonary artery as well as the conus of the right ventricle was prominent. *Subsequent Course:* Under rest and digitalis the pain and cough improved. It was thought by some observers at this time that he had a mediastinal tumor, and he received a prolonged series of x-ray treatments with no obvious change in the size of the chest mass. He has continued to be ambulatory and his fibrillation is easily controlled. *Diagnosis:* Rheumatic heart disease; mitral stenosis; extreme dilatation of left auricle; auricular fibrillation.

CASE 4.—C. H. A male of forty-seven years entered Philadelphia General Hospital in February, 1931, complaining of cough, shortness of breath and difficulty with

Fig. 7.—Case 5. Left ventricular hypertrophy. Left auricle extending far to the right and forming the major portion of the right border of the heart. Note prominence of conus on the upper left border of the heart.

swallowing. He denied all previous illness, having been well up to five months before admission. *Examination:* There was no evidence of dyspnea or cyanosis while the patient was lying comfortably in bed. The pulse was completely irregular. There was slight bulging of the precordia with a diffuse palpable impulse. Broadbent's sign was present. The apex was in the sixth intercostal space at the anterior axillary line, and dullness was present to the right of the sternum in the second and third intercostal spaces. There were a rough systolic apical murmur and a definite low-pitched rumble in diastole. A rough systolic murmur was heard at the aortic area. At the right base posteriorly there was relative dullness, diminished breath sounds but no moisture. Electrocardiogram showed auricular fibrillation. *X-ray Examination:* The heart was greatly enlarged in its transverse diameter (Fig. 5). In the right oblique position there was definite encroachment on the midportion of the retrocardiac space. There was a definite impression in the lower portion of the esophagus, and the barium was partially obstructed (Fig. 6). There was considerable dilatation above the obstruction, and the esophagus was displaced

posteriorly. *Subsequent Course:* Under rest and digitalis he improved, but due to definite delay to the barium in the esophagus, which amounted to almost complete obstruction at its middle third, he was sent to the Radium Clinic for treatment of a possible malignancy of the esophagus. His condition remained unchanged, although under proper digitalization he was able to eat with less difficulty. He continues to be ambulatory but with definite restriction of his activity. *Diagnosis:* Rheumatic heart disease; mitral stenosis; enlarged left auricle causing esophageal obstruction.

CASE 5.—C. M. A male aged thirty-three years entered the Philadelphia General Hospital in February, 1932, complaining of pain in the right chest, cough, breathlessness and moderate weakness. At the age of eighteen he had a severe pleurisy, followed by frequent colds but no rheumatic fever. *Examination:* Well-developed white male who showed no evidence of congestive heart failure. The heart was markedly enlarged to both the right and the left. The apex was palpable in the fifth space at the anterior axilla, with a diffuse impulse in the third and fourth interspaces to the left. Dullness extended to the right of the sternum beyond the nipple line in the fourth interspace. There was a definite palpable systolic pulsation in the right axilla in the fourth interspace. There was no thrill but at the apex the first sound was sharp and had a presystolic accentuation, followed by a short systolic murmur. The lungs were clear except for diminished expansion and suppressed breath sounds over the right base posteriorly. The pulse was completely irregular and the electrocardiogram showed auricular fibrillation. *X-ray Examination:* The heart was enormously enlarged, reaching nearly to both axillary borders (Fig. 7). The pulmonary artery and conus of the right ventricle were very prominent and showed marked pulsations fluoroscopically, whereas the right border showed feeble pulsations. In the right oblique view the left auricle filled the retrocardiac space, and the esophagus was displaced posteriorly and to the right. There was no obstruction to the flow of barium in the esophagus. *Subsequent Course:* Under rest and control of the ventricular rate by digitalis, his improvement was marked. He became ambulatory, was allowed up and eventually was discharged with only moderate restricted activity. *Diagnosis:* Rheumatic heart disease; mitral stenosis; extreme dilatation of the left auricle; auricular fibrillation.

DISCUSSION

Anatomy. The left auricle makes up the posterior and superior parts of the heart; it thus lies directly posterior and is at the same time the uppermost chamber of the heart. The tracheal bifurcation lies just above it and its left branch normally rests upon it. Directly behind the left auricle lies the esophagus, which is in contact with the pericardium over it for several centimeters. Since the auricle lies posteriorly, it may enlarge either to the right or to the left but more easily to the right. When the right ventricle enlarges, the heart is pushed into an abnormal position, because it cannot enlarge in a forward direction. There results an actual rotation of the entire heart to the left, and this carries the left auricle to the right, and it comes to lie somewhat transversely across the spinal column. The left auricle can attain a greater dilatation than any other chamber of the heart. The explanation for this lies in its thin walls, the absence of safety valves into the great veins as in the right auricle and because it is often being filled by both ventricles at once when there is mitral disease. In mild degrees of enlargement the auricle extends backward beneath the bifurcation of the trachea. When the

dilatation increases it fills the space beneath the arch of the aorta, which passes over and then down, behind it, and to its left. The left ventricle is in front, often enlarged and not infrequently rotated posteriorly also as a result of the right ventricular hypertrophy. The left auricle is therefore prevented from dilating to the left, since it cannot expand through the arch of the aorta. Being also against the spine behind, it enlarges to the right, forward and upward. The right auricle now lies in front of the left, slightly below it, and the right lung if free of adhesions is easily displaced toward the right axilla.

Pathology. What is the pathology underlying this remarkable dilatation? It would seem to be due not to any one factor but to a peculiar combination of lesions, which damages one portion of the myocardium far in excess of others, leaving the remaining myocardium relatively intact and capable of maintaining an efficient circulation. In nearly all reported cases, extreme dilatation of the left auricle to the right has been associated with mitral stenosis and often with some degree of adherent pericardium. In four of our cases there were present all the physical findings of a high grade of mitral stenosis. The fifth case, on physical findings, would be classed as a moderate stenosis. That the mechanical factor is not the specific influence in the dilatation is easily realized when we consider how common mitral stenosis and insufficiency are and how rarely extreme dilatation of the left auricle is seen. In order for the auricle to dilate to this extreme degree it seems necessary for the auricular myocardium to be replaced by a tissue with relatively little elasticity. This is no doubt the basis of the pathology. The brunt of the rheumatic carditis which attacks these hearts is borne by the auricle, while the ventricle remains relatively intact. The rheumatic infection acting upon the auricle over a long period of time produces a myocarditis with gradual replacement by fibrous tissue. It is well known that the rheumatic toxin has a predilection for the walls of small blood vessels; these are often occluded, and, if the process is a gradual one, fibrous tissue replaces the auricular myocardium without an intervening stage of necrosis such as occurs with sudden occlusion. If this fibrosis is local, it may lead to aneurysmal bulging, as in a case reported by Lutembacher[12]; if more diffused, it may lead to extreme dilatation. Fibrous tissue possesses only a slight degree of elasticity and when distended, tends to remain so. When the normal safeguarding action of the muscle is lost, then the heightened auricular tension is allowed full sway and the extreme degree of dilatation discussed here may result.

Many of the reported cases show pericardial adhesions to the auricular wall, but dilatation can hardly be ascribed to the mechanical traction of such adhesions. Naturally an adherent pericardium over the auricular wall would lead to underlying fibrosis but would tend more to limit dilatation than to cause it. We have been unable to find a case reported where extreme auricular dilatation has accompanied chronic pericarditis

involving an obliteration of the pericardial sac. Indurative mediastinopericarditis is usually associated with cardiac enlargement, but this is more liable to affect the right heart than the left. We doubt whether great cardiac enlargement is ever due to adhesion alone. The most reasonable basic explanation of this peculiar dilatation is a replacement fibrosis of the auricular wall, as first suggested by Bramwell and Duguid.[8]

The left ventricle in most of the reported cases is greatly hypertrophied and in four of our cases is apparently very large. This is certainly of extreme importance, for we believe a forceful left ventricle is essential to development of this condition. It acts in two ways. Having largely escaped the rheumatic infection, it is capable of maintaining an efficient circulation and by its vigorous action causes an increase in intra-auricular tension. It is this auricular tension acting upon a fibrous and distensible auricle which brings about this peculiar picture.

That stenosis of the mitral valve is not a necessary factor in causing left auricular dilatation is shown by the case described by Boch and Keith,[16] where huge dilatation of the auricle occurred, and yet the mitral valve was not stenosed but was thickened, producing a high degree of incompetency. Emanuel[2] reports two hearts showing marked auricular dilatation yet the mitral orifice readily admitted three fingers. If the lesion described as replacement fibrosis is present in the auricular wall, mitral incompetency is just as capable of producing left auricular dilatation as stenosis; probably more so, since intra-auricular pressure would be higher. In fact, Peel[10] has reported a case in which dilatation of the auricles, sufficient to produce pressure symptoms suggesting a mediastinal tumor, arose from a case of heart-block without valvular lesions. Here again intra-auricular tension would be greatly increased.

Physical Signs and Symptoms. These cases present the usual symptoms associated with rheumatic carditis and the physical signs diagnostic of mitral disease. Special symptoms, however, often arise. Difficulty and pain in swallowing may be marked, as in Cases 1 and 4. This difficulty in swallowing may be extreme and lead to surgical intervention. Rösler and Weiss[17] reported a series of cases in which difficulty in swallowing was a prominent feature. Pain in the chest is another common symptom and may be felt in the right axilla, at the base of the right lung or under the right breast. Cough is often severe and is caused by pressure upon the tracheal bifurcation or upon the left main bronchus.

This condition may entirely escape recognition, and its early diagnosis is only made possible by radioscopic examination. When the left auricle has dilated sufficiently to bring it near the right chest wall, then the signs will be more suggestive. To the right of the sternum in three of our cases a variable area of dullness could be mapped out. This dullness may extend into the axilla or even to the base of the right lung and be interpreted as due to pleural effusion. Over this area of dullness to

the right a systolic murmur is often heard distinctly, and there may be felt in some cases a systolic thrill. These signs are obviously due to regurgitation of blood into the auricle from the powerful left ventricle. The dullness of the heart to the right may not extend completely across the front of the chest into the axilla, but the heart dullness may be separated from the dull area in the axilla by an area of lung tympany, caused by a compression of the lung anteriorly by the enlarging left auricle. Again the heart sounds and murmurs may be heard with great intensity over the back. The anatomical relations are such that when the heart comes in direct contact with the vertebral column, the sound vibrations transmitted to the bony framework of the thoracic cage may account for the extensive area over which the systolic murmur is clearly audible. Three of our cases showed a decreased expansion of the right lower lung which must be the result of both bronchial and lung compression. In all of these three cases of great auricular dilatation, fibrillation of the auricles was present, and this has been true of most reported cases. It does not, however, seem to be a factor in the dynamics of the condition. In fact it would be most surprising if the auricles did not fibrillate when we consider the underlying pathology. The walls of the auricles, converted as they are into fibrous tissue, would seem incapable of transmitting a normal auricular impulse which depends upon continuity of muscle fibers. Since it takes but a small mass of auricular muscle to provide the path of a circus movement, we should expect fibrillation in all cases. It is true that the right auricle is often distended in fibrillation, but we have never seen a case in which the right auricle caused a palpable pulsation to the right of the sternum or in the axilla. In our three cases showing the greatest left auricular distention there was no congestive heart failure present. The greatly hypertrophied left ventricle being relatively free from disease is capable of maintaining a normal cardiac output and an efficient circulation.

Exercise Tolerance. One of the most interesting features in many of these patients with auricular dilatation is the extraordinary amount of physical activity of which they are often capable. Three of our patients showing the most extreme degree of dilatation of the auricle were able to carry on a fair degree of physical activity in spite of their valvular diseases and fibrillation. The patient in Case 2, whose heart is shown in Fig. 2, is still earning his living doing clerical work. In the two cases shown in Figs. 4 and 7 the patients are able to visit the Cardiac Clinic weekly.

The capacity of the normal auricle is considered to be between two and four ounces, yet the capacity of these greatly dilated auricles may be as much as thirty or forty ounces. The result of this storage of blood apart from the actual mechanical process of distention would be to increase tremendously the intra-auricular tension. Normally the effective pressure in the auricle is considered to be 50 mm. of water. Auricular

systole in itself plays but a small part in ventricular filling, although Straub[18] states that it supplies 50 per cent of the volume, while the figures of Wiggers[19] are somewhat lower. The part played by auricular systole varies with the length of diastole, but we know that hearts may function fairly efficiently without auricular systole. The question of this heightened auricular tension upon ventricular output is important in explaining both the absence of congestive failure and the excellent circulation shown under these apparent handicaps. Wiggers[19] has clearly demonstrated that the systolic ventricular discharge increases progressively as venous pressure increases, and this no doubt holds for these cases. Even with narrowed mitral orifices the high intra-auricular tension will enable the ventricles to become filled during diastole, and thus the heart can maintain an efficient output. Obviously each heart has a limit beyond which such effects are no longer obtained, the limit of adaptability depending upon venous return and the cardiac muscle's condition. Our observation would lead us to believe that as long as the cardiac muscle remains efficient, the increased volume of blood contained in the left auricle is accommodated by the great expansion of its walls and that no "back pressure" effects or congestive phenomena result in the pulmonary artery or right heart.

Radioscopic Diagnosis. Radiology was long ago first applied to the diagnosis of cardiac disease, but it is still too infrequently used as part of the systematic examination. Properly used it gives as much useful information as does electrocardiography. In the diagnosis of auricular enlargement, screening of the patient is essential to a correct interpretation. When the patient faces the screen, the right border of the heart shadow is generally formed entirely by the right auricle, but under pathological conditions, where hypertrophy involves both ventricles, the lower part of the border may be formed by the right ventricle. The pulsations of the right ventricle are synchronous with the left so that the shadow of the right ventricle can be distinguished from the auricle. In mitral lesions the left auricle is the first chamber to undergo hypertrophy and dilatation. As the pressure increases in the lesser circulation the right ventricle becomes enlarged. The right ventricle forming as it does the major portion of the anterior surface of the heart, being limited by the sternum anteriorly and the diaphragm inferiorly, cannot enlarge in a forward direction. As it enlarges, it rotates the whole heart and causes the conus and pulmonary artery to be pushed upward and to the left, and the left ventricle to be carried posteriorly. Due to the rotation of the heart the knob of the aorta becomes less prominent when viewed anteriorly. The left auricle which is always posterior, never forming part of the left cardiac silhouette, goes more to the right as it enlarges, because it cannot enlarge to the left and anteriorly due to the position of the left ventricle, while posteriorly the spine and aorta limit its expansion. In the right oblique position it will be seen first

encroaching on the midportion of the retrocardiac space, and later when it further enlarges it fills the midportion of this space, the upper and lower portions remaining clear. In posterior anterior views the left auricle as it goes to the right will first be seen as a denser shadow through the less dense right auricle. As it still further enlarges, it overrides the right auricle; only the lower portion of the right border of the heart is now formed by the right auricle. With further enlargement, the left auricle passes beyond the right auricle, and in the posterior anterior view the denser left auricle can be distinguished from the less dense right auricle, particularly when the Bucky diaphragm is used. That this large shadow to the right is not the right auricle is shown by the absence of signs of right auricular distention, such as jugular enlargement, pulsating liver, and centrifugal venous pulse. All of these would certainly be present were the right auricle distended to this degree.

Fluoroscopically, the right side of the heart shows very little pulsation as compared with that of the left side. The pressure on the trachea which develops in this condition makes the angle between the main bronchi more obtuse than normal. The study of the barium filled esophagus and its relation to the heart, aorta, and particularly the left auricle is very interesting and helpful. Displacement of the esophagus can be readily demonstrated, being always backward and to the right in mitral disease. This should be routinely studied in such cases, since in cardiac enlargement from other causes, the left auricle is rarely involved. The normal esophagus when viewed from the front inclines slightly to the left of the midline from the neck to the fourth thoracic vertebra. Here, as the aortic arch passes on its left, the esophagus regains the midline and bears slightly to the right. Below this, it again curves to the left, and in the lower portion it crosses in front of the descending aorta, bearing to the left until it enters the diaphragm. The patient should be examined during the act of swallowing a thick barium paste: this will cling to the walls of the esophagus for several minutes and all relations can be studied. The enlarged left auricle presses the esophagus backward and to the right; the pulsations of the auricle transmitted to the barium in the esophagus are striking. When such pulsations are present, they are always systolic in time and are obviously produced by the regurgitation of blood through the mitral orifice, since the greatly dilated auricle in fibrillation is incapable of pulsation. The esophagus will curve backward along the auricular wall; there will be a delay in the passage of the barium paste at the upper level of the auricle, and in the first right oblique position the barium will be seen to trickle in a thin stream around the convex auricular border.

Parkinson and Bedford[20] have shown that there may be three distinct impressions upon the barium filled esophagus when viewed in the first oblique position: first, the aortic impression, or the first curve, produced by the aortic arch as it passes backward; second, the pulmonary

artery impression, or the middle curve, due to the pressure of the left bronchus, right pulmonary artery, and the main pulmonary stem; the third impression, or the lower curve, produced by the large left auricle when present. In mitral disease, the impression made by the left auricle and the pulmonary artery is very marked.

SUMMARY

Five cases showing unusual dilatation of the left auricle have been described. In two of these esophageal obstruction was produced—in one case so pronounced as to lead to gastrostomy. In three of these cases, the left auricle extended far to the right and formed a portion of the right cardiac border. Early in the disease, x-ray examination is essential for the correct diagnosis, but in later stages diagnosis may be suspected clinically from fairly suggestive physical findings. The symptoms, physical findings, pathology, and vascular dynamics of this condition are reviewed. It is practically always seen in rheumatic hearts, with mitral stenosis and auricular fibrillation. The exercise tolerance and lack of congestive failure in some of these cases are quite remarkable.

REFERENCES

1. Owen, Sir I., and Fenton, W. J.: Clinical Society Trans. **34**: 183, 1901.
2. Emanuel, J. G.: Extreme Dilatation of the Left Auricle, Lancet **1**: 591, 1923.
3. Shaw, H. Batty: Horizontal Dilatation of the Left Auricle, Lancet **2**: 493, 1924.
4. East, C. F. T.: Great Dilatation of the Left Auricle, Lancet **1**: 1194, 1926.
5. Mahaim, I.: Aneurism of the Left Auricle, Medicine **10**: 210, 1929.
6. Bedford, D. E.: Extreme Dilatation of the Left Auricle to the Right, Amer. Heart J. **3**: 127, 1927.
7. Goedel, A.: Eine ungewohnliche Form der Herzvergrösserung bei Mitralstenose, Wien. klin. Wchnschr. **42**: 427, 1929.
8. Bramwell, J. Creghton, and Duguid, J. B.: Aneurysmal Dilatation of the Left Auricle, Quart. J. Med. **21**: 187, 1927.
9. Rosselet, A., and Boch, E.: Un cas d'anévrisme de l'oreillette gauche, Arch. d. mal. du coeur **17**: 145, 1924.
10. Peel, A. A. F.: Dilatation of the Auricles Resulting From Heart-Block, Lancet **2**: 1248, 1929.
11. Schott, A.: Extreme Dilatation of Left Auricle, Klin. Wchnschr. **3**: 1067, 1924.
12. Lutembacher, R.: Anévrisme de l'oreillette gauche, Arch. d. mal. du coeur **10**: 145, 1917.
13. Burkhardt, E. A., Jr.: Marked Dilatation of Left Auricle of Heart: Case Report, Am. J. Path. **6**: 463, 1930.
14. Steel, David: Extreme Dilatation of the Left Auricle, Am. J. Roentgenol. **26**: 1, 1931.
15. Bordet, E.: Les Anomalies de développement du profil de l'oreillette gauche dans le rétrecissement mitral, J. de méd. (ser. 2) **41**: 227, 1922.
16. Boch, F., and Keith, I. S.: Enlargement of the Left Auricle of the Heart, Lancet **2**: 766, 1929.
17. Rösler, H., and Weiss, K.: Ueber die Veräm derung des Öesophagusverlaufes durch den Vergrösserten linken Vorhof, Fortschr. a. d. Geb. d. Röntgenstrahlen **33**: 717, 1925.
18. Straub: Deutsches Arch. f. klin. Med. **115**: 531, 1914; **118**: 214, 1916.
19. Wiggers, Carl J.: Circulation in Health and Disease, 1923, pp. 105-115, Philadelphia, Lea and Febiger.
20. Parkinson, John, and Bedford, D. E.: Pulmonary Artery Impression on the Esophagus, Lancet **2**: 337, 1931.

SPONTANEOUS RUPTURE OF THE AORTA*

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SPONTANEOUS rupture of the aorta, exclusive of aneurysm, is almost never diagnosed antemortem; hence it is seldom met with in private practice or in the hospital. It is not a great rarity, however, on a busy autopsy table, where it is seen frequently enough to justify bearing such a possibility in mind at the bedside in a differential diagnosis in cases simulating coronary thrombosis, angina pectoris, and shock, and in cases of sudden death.

In the autopsy room of Erdheim's Pathological Institute at the City Hospital in Vienna, where 2500 to 3000 necropsies are performed yearly, four or five cases of ruptured aorta are seen every year. Ames and Townsend[1] and Oppenheim[2] state that spontaneous rupture of the aorta is met with once in five hundred autopsies. It is much more common than rupture of the heart; yet one rarely finds a detailed description of its etiology, symptomatology, and pathology in a textbook of medicine or of heart disease, or even in a textbook of pathology. At best it is mentioned and discussed in a paragraph or two. However, the literature on the subject is fairly rich, especially of single case reports found on postmortem examination, to the astonishment of the clinician. Recently the subject has been studied carefully from the etiological and pathological standpoints by Oppenheim,[2] Gsell,[3] Erdheim,[4] and Levinson.[5]

Boestrom,[6] Paschkis,[7] Oppenheim,[2] Letterer,[8] Osler[9] and many others claim that a normal aorta under certain conditions can rupture spontaneously. Just how does such a thing take place? What is the modus operandi? What is the mechanism of this fatal condition, and what is the sequence of events?

For some unknown reason, owing either to a sudden strain during emotional tension, or as a result of other change in the hemodynamic system, the blood pressure in the aorta rises abruptly. If the limit of the elasticity of the tube is surpassed, the wall breaks, and thereby the pressure is reduced. Now, if the force that produces the tear in the wall of the vessel is strong enough, or the resistance low enough, all three layers of the tube break. The result is instantaneous death. If, however, the force is weaker, or the resistance of the outer coats of the wall higher, the ensuing anatomical as well as symptomatic course can be divided into two stages. Anatomically, the precipitating factor of this deadly event produces a partial rupture or tear in the wall; that is, only the

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intima and media suffer a break. This break takes place in from 75 to 90 per cent of the cases at the weakest point of the aortic tube, approximately 1 to 4 cm. above the valve, as demonstrated mechanically by Oppenheim.[2] The break is also most commonly on the posterior wall and is transverse. Blood now enters between the layers of the media and adventitia and is propelled further by every systole of the heart and recoil of the aorta. This produces a wider and longer separation of the two layers, and this separation advances with the increase of the quantity of blood in the newly formed space. A so-called dissecting aneurysm, first described by Laennec, is thus formed. According to Aschoff[10] this is not a true dissecting aneurysm, as it has no second opening into the tube. Aschoff prefers to call it an intramural hematoma. As the pressure rises in this intramural hematoma, any additional strain resulting from muscular effort, or a physiological response such as a sneeze, cough, or even a strain at defecation, may produce a secondary rupture—the second stage in this most serious event.

If this secondary rupture is brought about gradually and into the inside of the tube, that is by another opening through the media and intima, a true dissecting aneurysm is formed, which, according to Boestrom,[6] Laves,[11] and Alfejev,[12] may heal. However, in about 90 per cent of the cases, the secondary rupture is to the exterior of the tube, and in 75 per cent of such instances into the pericardium, with resulting instantaneous death.

Symptomatically, at the time of the primary rupture the individual collapses or goes into shock. After recovery from collapse, he gives a history of having been seized by sudden severe pain in the chest and at a corresponding region in the back, followed by faintness or collapse. The patient appears apprehensive, dyspneic, and either cyanotic or pale, usually the latter. He complains of pain, shortness of breath, and dysphagia. On physical examination there is usually a loud prolonged systolic murmur at the aortic valve and also in the back. There may be a thrill at the aortic valve region. X-ray examination of the cardiac region may show a widened arch, ascending or descending aorta. The blood pressure is not characteristic. A diagnosis of angina pectoris, coronary thrombosis, aortic stenosis, ruptured aneurysm, or ruptured heart is usually made.

Under rigid precautions of absolute rest and immobilization it is conceivable and possible that the secondary rupture in the second stage of this event may take place on the inside of the aorta, with resulting healing. Indeed, Boestrom[6] reports 18 healed dissecting aneurysms out of 178 cases studied; but, as already mentioned, in 90 per cent of the cases the secondary rupture is to the exterior of the vessel, that is, through the adventitia either into the mediastinum or into the pericardium; or, if the primary tear was in the abdominal aorta, into the subperitoneal

spaces. Sudden death may ensue, therefore, when the patient is apparently on the way to improvement. Such a case is here reported:

An American seaman, J. R. W., aged fifty years, single, was admitted, ambulatory, to the U. S. Marine Hospital, Ellis Island, New York, October 8, 1931, at 4 P.M. His family history was irrelevant. He had had gonorrhea several times, the last occasion being in 1921. He had rheumatism at the age of thirty-eight years, being ill for a year. He knew of no cardiac complications at that time and was free from symptoms and in "perfect health" until the day of admission to the hospital. He was a heavy drinker. His chief complaint on admission was pain in the chest and back, and weakness. On the day of onset, while walking on the street he felt suddenly as if an "electric shock" went through his body. Everything became black before his eyes, and he had to hold on to a wall to avoid falling. After a few minutes he came to himself but was dyspneic and weak. Pain in the chest and in the back began to be severe. He went to the outpatient department of the Public Health Service from which he was sent to the hospital at Ellis Island.

Physical examination on admission showed an exceptionally well developed and well nourished male of about fifty years, very uncomfortable and dyspneic and complaining of pain. He did not appear gravely ill. The physical findings were confined to the chest. The heart was moderately enlarged to percussion and there was increased supracardiac dullness. A snappy systolic thrill was felt in the second right interspace. The first sound was hardly audible and was followed by a rough, long, rumbling murmur which continued less loudly even after the second sound, which was accentuated and snappy. The murmur was heard best over the aortic valve and also in the back. There were occasional extrasystoles. The pulses were unequal in volume. There was no deficit. Blood pressure: right 155/70, left 140/85 mm. The pupils were equal; there was no tracheal tug. Tenderness along the spine from fourth to sixth thoracic vertebrae was elicited. There was slight pallor of the face. Moist râles in both bases of the lungs were heard the next day. The liver was barely palpable. There was no edema. The temperature was 99.6° to 100.8°; the pulse rate 90 to 110; respiratory rate 24 to 28. A tentative diagnosis of coronary disease with aortic stenosis on a rheumatic basis was made. The patient was given nitroglycerin and sedatives and put to bed.

The next day the pain was slightly less, but the shortness of breath was about the same. The urine was negative, and the white blood count was normal. Blood for Wassermann reaction was not taken.

X-ray films of the heart showed the following: Enlargement of the left ventricle, dilatation of the arch and descending aorta, giving the appearance of aortic valvular disease with aneurysmal dilatation of the aorta. Both lung bases showed congestion. Electrocardiogram of the three conventional leads revealed nothing more than high voltage, left axis deviation and an inverted T_3.

On October 10, the patient had less dyspnea, but his pain was getting worse. His blood pressure showed no change; temperature was 100°, pulse rate 100 to 110. Râles in both bases of the lungs persisted. Sedatives and nitroglycerin were continued.

The next day the patient felt much better. He was sitting up in bed and was discussing something with his neighboring patients when he was suddenly heard to groan and died instantly.

Autopsy showed the following: Both pleural cavities contain a slight amount of flocculent exudate. The lungs are congested and edematous and show patches of bronchopneumonic infiltration. The pericardial cavity contains 500 c.c. of clotted blood. The heart is enlarged and there is moderate hypertrophy of the left ventricle. All valves are normal. The coronary arteries are free and patent. On the posterior

aspect of the aorta 2 cm. above the middle aortic cusp is a transverse tear 3 cm. long, with clots of blood on the edges. There is another tear 1 cm. long on the adventitial and pericardial surface. This opening leads into the pericardial sac. The wall of the aorta down to the diaphragm is split between the media and adventitia; the space is filled with clotted blood. The abdominal organs show evidence of passive congestion. Macroscopically the aorta is normal in appearance, except for a few atheromatous patches in its lower thoracic portion. It is quite elastic.

Twenty-two serial sections were made of the aorta in the region of the rupture, and it was impossible to find any pathological changes such as suppurative areas, foci of necrosis, or mucoid degeneration to account for the rupture.

COMMENT

This case then showed no reason why the aorta should have sustained such an injury. This is not surprising when one reviews the literature on this subject. More than 200 cases have been reported since the middle of the eighteenth century. One learns, however, that not all investigators are agreed as to the pathological findings in such cases. Indeed there are now two schools of thought with respect to what causes spontaneous rupture of the normal aorta. One group, Gsell,[3] Erdheim[4] and Levinson,[5] claims that a normal aorta cannot rupture, and demonstrates definite pathological changes at the point of rupture. Another larger group, Boestrom,[6] Oppenheim,[2] Letterer,[8] Osler,[9] Paschkis,[7] Kutschera,[13] Griffiths,[14] and many others, repeatedly have failed to find any demonstrable changes, and they explain the rupture on a mechanical basis.

The early investigators of the nineteenth century insisted that there must be some disease in the wall of the aorta even though they could demonstrate nothing very definite; they ascribed rupture to minor changes such as superficial atheroma and hypertrophy of the left ventricle.

Up to 1800, only two cases are recorded in the literature. The first case was reported by Nichols[15] in 1761. He gave a brief account of a case of sudden death due to a ruptured aorta. Nichols found no demonstrable changes in the ruptured aortic wall.

An excellent description of a case of ruptured aorta in a woman of twenty-nine years in labor was given by Lynn[16] in 1789. He related the symptoms in great detail and noted the two stages described above. The primary rupture occurred during labor and manifested itself by shock and cessation of labor pains. A diagnosis of ruptured heart was made. The child was delivered with forceps but was dead. The patient, however, began to improve later, so much so that the diagnosis of ruptured heart previously made was given up on the seventh day following delivery. The second stage of the rupture took place thirteen days after delivery with sudden death. Autopsy showed that the aorta had ruptured into the pericardium. The author reported that no specific lesion was found in the wall of the aorta, but there was no doubt that there must have been some pathological change, as parts of the inner coat

showed actual inflammation. A careful study was not possible, on account of poor light and great haste to return the body to the relatives.

Rokitansky[17] in 1838 gathered eight cases and studied them from an etiological and a pathological standpoint. He stated that he found no proof of definite pathology in the wall of the aorta near the rupture, yet he concluded that a normal aorta could not rupture. Perhaps there was some developmental abnormality, he suggested.

Broca,[18] in 1852, reported one case of spontaneous rupture of the aorta of a man of twenty-nine years, and reviewed the pathological findings of 28 other cases. He and Rokitansky[17] stressed atheroma of the aortic wall and hypertrophy of the heart as causative factors in spontaneous rupture.

Willhelm Wollner,[19] in 1856, called attention to spontaneous rupture and its relation to general arterial disease. Woodward,[20] in 1875, studied spontaneous rupture of the aorta and came to the conclusion that rupture may occur in a normal aorta. Harrington,[21] in 1879, reported a case and found no pathological changes.

However, up to the time of Boestrom,[6] in 1887, the general opinion was held that a normal aorta cannot rupture, even though no one was really able to demonstrate any definite lesion at the site of the tear. Boestrom studied primarily dissecting aneurysms. This led him to the subject of ruptured aorta, as most of his dissecting aneurysms came from that source. From an exhaustive pathological study and a review of 178 collected cases he concluded that there was no demonstrable change in the wall of the ruptured vessel and, therefore, set down the rule that a normal aorta can rupture spontaneously, and that 75 per cent of the secondary ruptures take place in the pericardium. His opinion reigned supreme until the third decade of the twentieth century, when further studies were begun.

Ames and Townsend,[1] in 1897, published a case of spontaneous rupture and stated that to that date only 100 cases had been reported in all literature. They reviewed carefully 50 cases and came to the conclusion, despite Boestrom's opinion to the contrary, that an aorta can rupture only if it is diseased in one way or another. They added nothing to the indefinite pathological picture that had been described vaguely up to that time.

In the succeeding twenty years, and especially following the war, a large number of cases of spontaneous rupture of the normal aorta appeared in the literature. More than 100 cases were reported from 1900 to 1922, and many more since then.

The tide began to turn from Boestrom,[6] in 1906, when at the Tenth Pathological Congress at Stuttgart, the speakers discussed the subject of spontaneous rupture and were of the opinion that rupture of an aorta without underlying pathology was inconceivable.

This stimulated Oppenheim,[2] in 1918, to do an elaborate piece of work on this subject. After an exhaustive study of many serial sections of the walls of spontaneously ruptured aortae, he affirmed Boestrom's original contention that a normal, healthy aorta can rupture without rhyme or reason. In a further laborious and very ingenious piece of work he proceeded to investigate the mechanism and hemodynamics of this process. He wanted to know how and why the aorta usually ruptures at its ascending portion or at the arch. Following the lead of Flockerman,[22] in 1898, who showed that increased pressure in the left ventricle may cause rupture of the aorta, he proceeded to find the *locus minoris resistentiae* of this vessel. He took normal hearts and aortae from human bodies fresh from the autopsy table and subjected the vessel to a pressure of four atmospheres through a rubber tube inserted into the left ventricle. The aortae would invariably rupture at the ascending portion or at the beginning of the bend to form the arch where usually fatal ruptures take place. He also noticed that this portion of the tube suffered the greatest burden of stress and strain and, therefore, burst at this point when the limits of elasticity had been surpassed. He thus concluded that a sudden rise in blood pressure may tax the ascending portion of the aorta, which is the *locus minoris resistentia*, to such an extent that rupture must follow.

He also cited numerous reported cases of ruptured aortae in aviators falling from great heights, inferring that a fall from a great altitude produces a sudden and unusual rise in blood pressure which results in rupture of the aorta at the above mentioned place.

However, the aorta continued to be of interest to many pathologists and investigators. Numerous reports of various pathological processes in the walls of the aortae that did not rupture appeared in the medical journals. Thus Pappenheimer and von Glahn,[23] Maresh,[24] Chiari,[25] Eberhardt,[26] Koritschoner,[27] and Erdheim[4] reported a variety of pathological processes in the media and adventitia of the aorta that could easily have caused rupture of the vessel. Pappenheimer and von Glahn reported Aschoff bodies in the media in rheumatic fever cases; Maresh, Chiari, and Erdheim described foci of suppuration in the media; Cellina[28] and Erdheim medionecrosis and mucoid degeneration of the media.

In 1926, Gsell[3] studied serial sections of eight cases of spontaneous rupture and found medionecrosis, angiomalacia, and small areas of actual suppurative inflammation in the mediae of all his cases. He advanced the theory that chronic suppurations or toxic processes in the body, such as chronic nephritis, may have a causal relationship to the processes in the wall of the aorta.

In a more recent careful study of the pathology of this subject, Levinson[5] working in Erdheim's Pathological Institute in Vienna, reports six cases of spontaneous rupture from mild causes with microphoto-

graphic evidence of pathology in the media of every case. Levinson states that frequently the pathological process is so limited in extent and apparently so insignificant as to escape the attention of the most careful investigator unless serial sections are made extending from one extreme to the other of the tear. Such careful study necessitates as many as 50 to 65 sections. He finds that foci of suppurative inflammation, focal necroses, or mucoid degeneration of the media were present at some point along the tear in all cases studied. The tear is always larger than the pathological process. No definite organism was isolated.

Inasmuch as many investigators mentioned above have found more extensive pathological change in aortic walls of nonruptured cases, it is difficult to assume that an admittedly slight inflammatory condition or mucoid degeneration should be the whole story of the cause of spontaneous rupture.

Only one contribution was made with respect to symptomatology and physical signs as an aid in diagnosis, and that is by Conto.[29] He stresses sudden pain, cyanosis, a systolic thrill at the aorta and pulmonary valve, and a systolic murmur at that area as pathognomonic of rupture. In his cases, however, the ruptures took place into the pulmonary artery.

SUMMARY

A case is reported of spontaneous rupture of the aorta into the pericardium in which careful histological examination failed to reveal contributory pathological changes. Instances of such spontaneous rupture are not extremely rare, but the condition is practically never recognized during life. A review of the literature shows that such ruptures occur twice as frequently in males as in females; that age seems not be an important factor; that in many instances no changes have been found in the aortic wall and that most of such tears take place in the ascending aorta and are transverse. Usually the rupture involves at first only the intima and the media; the latter is then separated from the adventitia by a dissecting hematoma which ultimately ruptures through the adventitia at some distance from the point of the primary tear. Frequently the external rupture takes place into the pericardial sac. The symptoms and signs are discussed.

After this paper had been submitted for publication, an important article on "Spontaneous Rupture of the Aorta" by Klotz and Simpson[51] appeared, in which the pathological findings of five cases are carefully studied. The authors report noninflammatory degeneration of the media and elastic fibers in all their five cases.

REFERENCES

1. Ames and Townsend: Spontaneous Rupture of Aorta Exclusive of Aneurysms, Maryland M. J. **37**: 199, 226, 1897.
2. Oppenheim, Franz: Gibt es eine Spontanruptur der Aorta und wie kommt sie Zustande München. med. Wchnschr. **65**: 1236, 1918.
3. Gsell, Otto: Wandnekrosen der Aorta und ihre Beziehung zur Spontanruptur, Virchows Arch. f. path. Anat. **270**: 1, 1928.
4. Erdheim: Medionekrosis, Virchows Arch. f. path. Anat. **273**: 454, 1929.

5. Levinson, B.: Ueber tödliche Aorten Zerreissung aus geringen Ursachen, Virchows Arch. f. path. Anat. **282**: 1, 1931.
6. Boestrom: Das Geheilte Aneurysma dissecans, Deutsch. Arch. f. klin. Med. **42**: 1, 1888.
7. Paschkis, K.: Ueber Aortenruptur bei intakten Gefässwand, Med. klin. Berlin **21**: 1921, 1925.
8. Letterer, E.: Typische Stelle Aortenruptur, Virchows Arch. f. path. Anat. **253**: 534, 1924.
9. Osler: Modern Medicine, **4**: 85, 1927.
10. Aschoff: Pathologische Anatomie Siebente Auflage, Jena, Zweiter Band p. 82, 1928, Gustav Fischer.
11. Laves, W.: Ein Fall von ausgeheilter zirkulärer Ruptur der Aorta Ascendens mit sekundärer Aneurysm Abbildung, Wien. klin. Wchnschr. **37**: 804, 1925.
12. Alfejev, Frau S.: Zufälliger Befund eines Ausgeheilten Aortenrisses, Zentralbl. f. Herz.-u. Gefässkr. **15**: 33, 1923.
13. Kutschera: Ruptur der Aorta, Wien. med. Wchnschr. **77**: 263, 1927.
14. Griffiths, J. H.: Traumatic Rupture of Aorta, Brit. J. Surg. **18**: 664, 1927.
15. Nichols: Ruptured Aorta, Philosophical Transactions of 1761, **35**: 443, Abstracted by Ames and Townsend.
16. Lynn: An Account of a Ruptured Aorta, Medical Record and Researches of a Private Med. Association, **6**: 71, 1 pl., London, 1798.
17. Rokitansky: 1838, Abstracted by Ames and Townsend.[1]
18. Broca: Bull. Soc. Anat. de Paris **27**: 273, 1852. Reviewed by Ames and Townsend.
19. Wollner, W.: Monograph. Ueber die spontane Ruptur der Aorta und das Verhältnis der Arterienerkrankung überhaupt, Erlangen C. H. Kunstmann, **8**: 29, 1856.
20. Woodward: Trans. of M. Soc. Washington, D. C., **1**: 49, 1875.
21. Harrington: Spontaneous Rupture of Aorta, Chicago M. J. & Exam. **38**: 362, 1879.
22. Flockerman: Ueber Aneurysma dissecans, München. med. Wchnschr. **45**: 847, 1898.
23. Pappenheimer and von Glahn: Rheumatic Findings of Aorta, J. Metab. Res. **44**: 498, 1924.
24. Maresh: Eitrige Aortitis, Wien. klin. Wchnschr. **39**: 1078, 1926.
25. Chiari, H.: Ueber Veränderungen in der Adventitia der Aorta und ihrer Hauptäste im Gefolge von Rheumatismus, Beitrag. z. path. Anat. **80**: 336, 1928.
26. Eberhardt: Panaortitis, Zentralbl. Path. **38**: 261, 1926.
27. Koritschoner: Beitrag zur Kenntniss der mykotichen Aortitis, Zentralbl. Path. **23**: 100, 1912.
28. Cellina: Medionecrosis, Virchows Arch. f. path. Anat. **280**: 65, 1931.
29. Conto, M.: Spontaneous Rupture of Aorta, Bull. Acad. de méd., Paris, April, 1926, Abst. J. A. M. A. **86**: 1947, 1926.
30. Bohner, Paul: Rupture of Aorta During Pregnancy, Zentralbl. f. Gynäk. **51**: 96, 1928.
31. Walker, C. R. L.: So-Called Dissecting Aneurysm, Brit. M. J. **2**: 200, 1919.
32. McLean, J.: Spontaneous Rupture of Aorta, M. J. Australia **16**: 807, 1929.
33. Thorpe: Ruptured Aorta, Lancet **1**: 756, 1928.
34. Maitland, C. D.: Spontaneous Rupture of Aorta, Brit. M. J. **1**: 69, 1925.
35. Kahlden: Seltene Aortenruptur, Zentralbl. Path. **12**: 835, 1901.
36. Witte: Perforation der Aorta, Beitr. z. path. Anat. **37**: 151, 1905.
37. Loffler: Spontanruptur der Aorta bei chronischen Nephritis, Zentralbl. f. Inn. Med. **4**: 666, 1919.
38. Freiher Von Schnurbein: Ruptur der Aorta, Frankfurt. Ztschr. f. Path. **34**: 532, 1926.
39. St. George, A. V.: Spontaneous Rupture of Heart and Aorta, Am. J. Syph. **4**: 702, 1920.
40. Boy, H.: Zur Lehre der Spontanenruptur, Frankfurt. Ztschr. f. Path. **1**: 70, 1910.
41. Schachtelin: Plötzliche Todesfälle durch spontane Aortenruptur, Deutsche Ztschr. f. d. ges. gerichtl. Med. **5**: 532, 1925.
42. Busse: Ueber Zerreissung und traumatische Aneurysmen der Aorta, Virchows. Arch. f. path. Anat. **183**: 440, 1906.
43. Sheldon, H.: A Case of Ruptured Thoracic Aorta, Lancet **1**: 436, 1926.
44. Schoppler, H.: Aortenruptur, München. med. Wchnschr. **68**: 459, 1921.
45. Jenner: Beitrag zur Kenntniss der traumatischen Aortenruptur, Virchows Arch. f. path. Anat. **224**: 259, 1919.

46. Sternberg, H.: Ueber Fälle von Durchbruch der Aorta in die Arteria Pulmonalis, Wien. klin. Wchnschr. **32**: 1024, 1919.
47. Kortiger, E.: Aortenruptur auf tuberkulose Grundlage, Med. Klin. Berlin **6**: 361, 1920.
48. Jaffe and Sternberg: Ein Beitrag zur Frage der traumatischen Aortenrupturen, Vrtljschr. f. gerichtl. Med. Berlin **58**: 74, 1919.
49. Guttman: Perforation der Aorta in die Vena cava superior, Deutsche med. Wchnschr. **53**: 1473, 1927.
50. Rindfleisch: Zur Entstehung und Heilung des Aneurysma dissecans Aortae, Virchows. Arch. f. path. Anat. **131**: 374, 1893.
51. Klotz and Simpson: Spontaneous Rupture of the Aorta, Am. J. M. Sc. **184**: 455, 1932.

VARIATIONS IN POTENCY OF CERTAIN COMMERCIAL PREPARATIONS OF DIGITALIS*

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A STUDY was planned requiring the use of a soluble preparation of digitalis which could be administered by intramuscular or hypodermic injection. It seemed desirable, at the start, to determine, by the technic of biologic assay, the potency of certain available commercial products. The cat method of Hatcher and Brody[1] was employed. The results of these preliminary determinations were not in agreement with the advertised claims of the manufacturers, and the variations in potency of two preparations, as well as of different lots of the same product, were astonishingly great. The investigation was therefore extended to include all of the liquid preparations of digitalis, dispensed in ampules, which are listed in *New and Non-Official Remedies,* 1931 edition. For comparison, one British product and two specimens of commercial digitalis tincture were also tested. In view of the wide use which is made of digitalis dispensed in ampules and because of the dependence of the medical profession upon these products in times of emergency, the results of our observations are here made known.

THE STANDARDIZATION OF DIGITALIS

It is only in recent years that standardization of commercial digitalis, in this country, has become common practice. In the absence of a satisfactory chemical method of assay, the biologic technic has been employed, and, for practical purposes, has been found adequate. In short, a preparation found to be potent by biologic test proves, with rare exceptions, to be therapeutically effective.

The Pharmacopeia of the United States has made official in this country the one-hour frog method. But there are products on the market, which, according to their labels, have been assayed by the guinea pig technic or the cat method; and more recently potency has been expressed by one firm in terms of the international unit. Such lack of uniformity in standardization is confusing to the clinician, since the same amounts of preparations assayed by different methods have not the same therapeutic efficacy, and the practitioner of medicine can hardly be held responsible for translating the value of one unit into terms of another. Clearly, it is desirable that there should be agreement in this matter. There are many who are of the opinion that the cat method of Hatcher is at present the best available with respect to simplicity, accuracy and cheapness.

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The American Heart Association, through its Digitalis Committee, has expressed its approval of this method by distributing to its constituent cardiac clinics throughout the United States powdered digitalis leaf assayed by the cat technic and dispensed in tablets containing one cat unit. It is of significance also that the digitalis powder which, according to a decision reached at the Geneva Conference in 1925, shall serve as the international standard, was assayed by the Hatcher cat method, slightly modified by Magnus.[2]

It is now usual for the drug manufacturers to advertise the fact that their digitalis products have been standardized. A mere statement to this effect, however, is not sufficient; and it is essential, if accurate dosage is to be employed, that the results of assay be expressed in units applicable to the particular preparation described.[3] Some of the statements made in the advertising literature follow:*

(1) "Digifoline (Ciba) is of such potency that each cubic centimeter of the contents of the ampules is equivalent to 1½ grains (approximately 0.1 gram) of digitalis leaf standardized by the Focke method." "You may confidently choose each or all forms of Digifoline, Ciba, Doctor, with the knowledge that it is a *dependable* digitalis product."

(2) "Digitan (Merck)—a digitalis preparation of dependable potency, stable in composition, accurately assayed and physiologically standardized." "The liquid forms are equivalent, drop for drop, to a fully potent U. S. P. tincture of digitalis. One c.c. (16 minims) of these liquid forms is equivalent to 1½ grains of potent, dried digitalis leaves."

(3) With regard to Digalen, two different types of advertising must be quoted in fairness to the Hoffmann-LaRoche Co. In the summer of 1931, when this work was begun, the claims were as follows: "Digalen (Roche) can be depended upon to give prompt action whenever the heart can respond to digitalis." No specific mention was made of standardization and the circulars suggested that "the doctor give enough for effect and in amounts adjusted to *individual case requirement.*" More recently, this company has changed its policy with regard to digitalis. It is at present stated that: "The strength of Digalen in all forms is now declared in terms of cat unit potency." "We have selected the cat unit because of the increasing preference for it expressed by many cardiologists." "One ampule, 2 c.c. = 1 cat unit (cir. 150 frog units)."

(4) "Digitos (Mulford) is standardized by the lethal dose method on guinea pigs. The fatal dose for a 250 gram guinea pig is contained in one c.c." "All lots are fully and equally active." "The dosage of Digitos is the same as that of a standard tincture of digitalis."

(5) "Digitalin (Cryst.) (Burroughs Wellcome) 0.0001 gm. (gr. 1/640 approx.) in one c.c. (Alcohol 13.5 per cent). A sterilized solution specially prepared for hypodermic injection." "Made in England by the Wellcome Foundation Ltd. for Burroughs Wellcome and Co (U. S. A.) Inc."

(6) "Tincture Digitalis (Squibb) U. S. P. X. Fat free, Physiologically tested." This means that it has been assayed by the official frog method.

(7) "Tincture Digitalis (Lederle) is not official U. S. P. strength." "It is standardized by the cat method of Hatcher, as modified and approved by the International Conference on the Standardization of Biological Products. Its potency is

*These quotations are taken from advertisements appearing in current medical journals and from circulars supplied by the manufacturing drug companies.

adjusted to a content of 1.5 cat units per cubic centimeter (15 minims)." "It is somewhat stronger than U. S. P. Tincture." "It has dependable and uniform activity."

To what extent claims for dependability, uniformity and potency are justified, is apparent from a perusal of Tables I and II.

ANALYSIS OF RESULTS

A. *Ampule Products.* It is obviously difficult to compare in a just manner a series of products prepared in various ways and assayed by different methods. For purposes of discussion, 100 per cent potency has been assumed when the cat unit was equivalent to one cubic centimeter of the liquid under examination. This assumption is entirely arbitrary, but is based on the fact that one c.c. (15 minims) of U. S. P. tincture, which is the commonly employed clinical unit of dosage in this country, contains approximately one cat unit. Three facts are immediately apparent: (1) with two exceptions to be discussed further, all lots of the various commercial preparations were below the expected potency, as estimated according to the claims in their advertising literature; (2) there was a wide range of activity in preparations manufactured by the various commercial houses; (3) in four instances, different lots of the same product were not of uniform potency, in terms of cat units.

Thus, the percentage potency of Digifoline ranged, in different lots, from 23 to 46; Digalen from 41 to 72; Digitalin from 18 to 19; and Digitos from 15 to 45. One lot of Digitan was 97 per cent of the estimated standard strength; another lot assayed only 68 per cent, according to the same estimated standard.

The Burroughs Wellcome product merits a word of special comment. It is labeled "Digitalin (Cryst.)," which, according to Merck's Index,[4] is synonymous with digitonin, a glucoside which has no physiologic action on the heart. The digitalis principle contained in these ampules is clearly the crystalline "digitaline" of Nativelle, subsequently called "digitoxin" by Schmiedeberg.* In order to administer one cat unit of this incorrectly designated preparation, it is necessary to inject more than 5 c.c. of the liquid. Assuming that 0.1 mg. of digitoxin were present in one c.c., as stated on the box, the cat unit should be 3 c.c. instead of 5 c.c., since the cat unit value of the crystalline substance is 0.3 mg.[1] Even in terms of the manufacturer's standards, the contents of the ampules are only 60 per cent potent.

Specimens of Digalen, in ampules, purchased in 1931, ranged in potency from 41 to 72 per cent of the standard. The newest preparation, said to be standardized by the cat method, was 171 per cent of its actual labeled potency, in terms of cat units. From the Medical Director of Hoffmann-

*A letter from Burroughs Wellcome and Co., in reply to an inquiry concerning Digitalin (Cryst.) states that "this substance is official in the French Codex and corresponds to the German Digitoxin." "In cases of asystole amenable to digitalis an injection is made for four consecutive days. In milder cases of hyposystole, on two consecutive days, one c.c. being the injection in each case."

TABLE I

BIOLOGIC STANDARDIZATION OF COMMERCIAL PREPARATIONS OF DIGITALIS (IN AMPULES) BY THE CAT METHOD OF HATCHER AND BRODY

CAT NO.*	PREPARATION	LOT NO.	CAT WEIGHT KG.	DOSE C.C.	INJECTION TIME¶ HR.	INJECTION TIME¶ MIN.	CAT UNIT C.C.	% OF POTENCY COMPARED TO U. S. P. TINCTURE†
1	Digifoline (Ciba)	0683	2.90	5.0		52	1.72	58.0
2	Digifoline (Ciba)	0683	2.95	6.0	1	14	2.03	49.2
3	Digifoline (Ciba)	0683	4.18	10.0	1	25	2.38	42.0
4	Digifoline (Ciba)	0683	3.55	8.5	1	29	2.39	41.8
5	Digifoline (Ciba)	0683	3.25	7.5	1	37	2.31	43.3
6	Digifoline (Ciba)	0683 07983	3.35	6.0	1	40	1.79	55.8
7	Digifoline (Ciba)	0683	4.12	10.0	2	50	2.42	41.0
Average	Digifoline (Ciba)	0683					2.15	46.5
1	Digifoline (Ciba)	07983	4.22	17.5	2		4.15	24.0
2	Digifoline (Ciba)	07983	3.58	16.5	4	20	4.61	21.8
Average	Digifoline (Ciba)	07983					4.37	22.9
1	Digitan (Merck)	30521	3.65	4.0		38	1.10	90.9
2	Digitan (Merck)	30521	4.20	3.4		58	.81	123.5
3	Digitan (Merck)	30521	4.00	4.0	1	09	1.00	100.0
4	Digitan (Merck)	30521	4.10	3.6	1	24	.88	114.0
5	Digitan (Merck)	30521	3.25	3.6	1	30	1.11	90.1
6	Digitan (Merck)	30521	4.25	5.0	1	30	1.17	85.5
7	Digitan (Merck)	30521	3.45	4.0	1	49	1.16	86.0
Average	Digitan (Merck)	30521					1.03	97.0
1	Digitan (Merck)	32840	3.22	4.0	1	11	1.24	80.0
2	Digitan (Merck)	32840	3.02	4.0	1	12	1.33	75.0
3	Digitan (Merck)	32840	3.85	6.0	1	37	1.56	64.2
4	Digitan (Merck)	32840	2.95	5.0	1	40	1.70	59.0
Average	Digitan (Merck)	32840					1.46	68.5
1	Digalen (Roche)§	204169	2.95	7.0	1	32	2.37	42.1
2	Digalen (Roche)§	204169	2.75	6.5	1	39	2.36	42.3
3	Digalen (Roche)§	204169	3.50	8.0	2		2.29	43.8
4	Digalen (Roche)§	204169	3.45	9.0	2	12	2.61	38.3
Average	Digalen (Roche)§	204169					2.41	41.6
1	Digalen (Roche)§	311030	3.43	5.0	1	25	1.46	68.6
1	Digalen (Roche)§	311130	3.62	5.0	1	17	1.38	72.4
1	Digalen (Roche)‖	311191	2.90	3.6		48	1.17	171.0
2	Digalen (Roche)‖	311191	3.55	3.7	1	02	1.05	190.4
3	Digalen (Roche)‖	311191	3.75	4.5	1	17	1.23	162.8
4	Digalen (Roche)‖	311191	4.10	4.5	1	28	1.10	182.0
5	Digalen (Roche)‖	311191	2.75	3.5	1	30	1.28	156.2
Average	Digalen (Roche)‖	311191					1.17	170.9
1	Digitalin (Burroughs-Wellcome)	15004	3.05	15.0		57	4.92	20.3
2	Digitalin (Burroughs-Wellcome)	15004	4.40	23.0		59	5.23	19.1
3	Digitalin (Burroughs-Wellcome)	15004	3.70	19.5	1	02	5.27	19.0
4	Digitalin (Burroughs-Wellcome)	15004	4.10	21.5	1	08	5.24	19.0
5	Digitalin (Burroughs-Wellcome)	15004	3.22	21.0	2	44	6.52	15.3
Average	Digitalin (Burroughs-Wellcome)	15004					5.44	18.5

TABLE I (CONTINUED)

CAT NO.*	PREPARATION	LOT NO.	CAT WEIGHT KG.	DOSE C.C.	INJECTION TIME¶ HR.	INJECTION TIME¶ MIN.	CAT UNIT C.C.	% OF POTENCY COMPARED TO U. S. P. TINCTURE†
1	Digitalin (Burroughs-Wellcome)	32513	2.5	12.0	1	24	4.80	20.4
2	Digitalin (Burroughs-Wellcome)	32513	3.1	16.5	1	32	5.32	18.8
Average	Digitalin (Burroughs-Wellcome)	32513					5.06	19.6
1‡	Digitos (Mulford)	700965A	2.45	4.0		43	1.63	61.3
2	Digitos (Mulford)	700965A	3.17	6.5	1	10	2.05	48.8
3	Digitos (Mulford)	700965A	3.13	6.5	1	21	2.09	48.2
4	Digitos (Mulford)	700965A	3.03	9.0	2	18	2.97	33.7
Average	Digitos (Mulford)	700965A					2.19	45.6
1	Digitos (Mulford)	675482A	3.4	9.0	1	23	2.65	37.8
1	Digitos (Mulford)	675482A 659933A	3.2	20.7	2	22	6.47	15.5

*Adult male cats used.

†One hundred per cent potency is assumed when one c.c. contains one cat unit. This assumption is arbitrary, and is based on the fact that one c.c. of U. S. P. tincture contains approximately one cat unit.

‡Not fully grown.

§Obtained in 1931. No reference to standardization.

||Obtained in 1932. Said to be standardized by the cat method and put up so that 2 c.c. equal one cat unit.

¶It has been shown that the injections may be made over periods varying from ten minutes to three or four hours, and the duration of the experiment, within these limits, exerts little or no effect upon the ultimate dose required. [Eggleston, C., Biological Standardization of the Digitalis Bodies by the Cat Method of Hatcher, Am. J. Pharm. **85**: 99, 1913.]

LaRoche, Inc., it was learned that these standardizations were carried out in the company's laboratories in Switzerland. Herein may lie one reason for variation. It has been shown that guinea pigs reacted differently to the same brand of neoarsphenamine when sensitization experiments were carried out in Breslau, Zürich and New York, in spite of care in providing for an identical technic. On the basis of these observations, Sulzberger and Mayer[5] point out that diet as well as other influences, such as nonhomogeneous races of laboratory animals, must be taken into account in the interpretation of experimental results in different localities. Furthermore, in the standardization of digitalis, Macht[6] found that biologic assays by the cat method varied with altitude and the state of the weather.

Quite recently, assays of various commercial preparations of digitalis have been carried out in Germany in a manner comparable to our own.[7] In the pharmacological laboratories of the Universities of Heidelberg, Leipzig, and Giessen, biologic assays of ampule products, liquid digitalis and tablets were made by the Straub-Houghton frog method. The figures obtained with the same products in the three laboratories were in close agreement. All of the preparations examined contained digitalis in amounts below the values ascribed to them by the manufacturers. For example, the liquid in an ampule of Digalen was 48 per cent of its supposed strength; Digifoline was 25 per cent potent; and Digipurat, which

TABLE II

BIOLOGIC STANDARDIZATION OF COMMERCIAL TINCTURES OF DIGITALIS BY THE CAT METHOD OF HATCHER AND BRODY

CAT NO.*	PREPARATION	LOT NO.	CAT WEIGHT KG.	DOSE C.C.	INJECTION TIME HR.	INJECTION TIME MIN.	CAT UNIT C.C.	% OF POTENCY COMPARED TO U. S. P. TINCTURE†
1	Tincture Digitalis (Squibb)‡	OK2384	3.53	3.0		51	0.849	117.7
2	Tincture Digitalis (Squibb)‡	OK2384	4.30	3.75	1	15	0.872	114.7
3	Tincture Digitalis (Squibb)‡	OK2384	3.27	2.80	1	16	0.857	116.8
4	Tincture Digitalis (Squibb)‡	OK2384	2.95	2.90	1	28	0.989	101.0
5	Tincture Digitalis (Squibb)‡	OK2384	4.50	4.75	2		1.05	94.4
6	Tincture Digitalis (Squibb)‡	OK2384	3.17	3.0	2		0.946	105.7
Average	Tincture Digitalis (Squibb)‡	OK2384					0.927	108.4
1	Tincture Digitalis (Lederle)‖	225H23H	3.10	1.50		44	0.484	137.8
2	Tincture Digitalis (Lederle)‖	225H23H	2.78	1.50		54	0.539	123.8
3	Tincture Digitalis (Lederle)‖	225H23H	3.10	1.40	1	19	0.453	147.2
4	Tincture Digitalis (Lederle)‖	225H23H	3.70	2.25	1	25	0.608	109.7
5	Tincture Digitalis (Lederle)‖	225H23H	4.70	2.50	1	30	0.532	125.4
6	Tincture Digitalis (Lederle)‖	225H23H	3.95	2.13	1	30	0.538	124.0
Average	Tincture Digitalis (Lederle)‖	225H23H					0.526	128.0

*Adult male cats used.

†One hundred per cent potency is assumed when one c.c. contains one cat unit. This assumption is arbitrary, and is based on the fact that one c.c. of U. S. P. tincture contains approximately one cat unit.

‡"*Tincture Digitalis*, U. S. P. X. Fat free. Physiologically tested." E. R. Squibb & Sons.

‖*Tincture Digitalis Lederle*, standardized May 12, 1930, obtained from Lederle Antitoxin Laboratories on June 8, 1931. "Fat free. Physiologically standardized by the cat method of Hatcher. One c.c. contains 1½ cat units." The cat unit, in this instance, should be 0.667 c.c. The per cent of estimated potency has been calculated on this basis.

is the German preparation of Digitan, was 92 per cent of its estimated potency. These figures for the ampule products approximate some of the assay values which we have obtained for preparations of the same name marketed in America. Different lots of the same preparation also showed wide variations in biologic activity. The German authors conclude that "the greatest variation from the average is far larger, in some preparations, than would be present in carefully prepared products."

B. *Tinctures.* The tinctures, in contradistinction to the ampule products, were fully potent. That of Squibb, standardized by the manufacturer by the one-hour frog method, yielded a value of 108 per cent; that

of Lederle, said to be standardized by the cat method, was 128 per cent of its labeled activity.

DISCUSSION

What are the possible causes for such variations in potency? Differences in the method of standardization first suggest themselves. Yet it is a fact that one cubic centimeter of a preparation properly standardized by the frog method is equivalent to one cat unit, as may be seen by referring to the results obtained with Squibb's tincture (Table II). Furthermore, variability of different lots of the same product cannot be accounted for on this basis.

It has been shown that aqueous solutions of crystalline strophanthin (Ouabain), put up and sterilized in soft glass ampules, deteriorate rapidly, due to a change in hydrogen-ion concentration toward the alkaline side, with resultant decomposition of the glucoside molecule.[8, 9] Such deterioration can be prevented by employing hard glass ampules and using a buffer solution (phosphate mixture of P_H 7.0) as solvent.[8]

Accordingly, determinations were made of the hyrogen-ion concentration of the contents of the various ampules containing digitalis (Table III). Of the five preparations examined, three were acid in reaction, one was sharply alkaline, and the fifth (Digitan, Merck), though slightly alkaline, more nearly approached neutrality. It is noteworthy that this latter preparation was the most potent of the group.

To what extent an acid or alkaline reaction may affect the strength of aqueous solutions of digitalis, particularly after sterilization by heating in a sealed glass container, we have not attempted to determine. After a study of the relationship of P_H to the potency of digitalis infusions, Tainter[10] concluded that the hydrolytic cleavage of the glucosides which goes on slowly at room temperature and the natural P_H, is accelerated by an increase in acidity or alkalinity as well as by a moderate increase in temperature. By analogy with the observations on crystalline strophanthin, it is reasonable to infer that changes in P_H may play a rôle, and that a sharply alkaline reaction particularly is to be avoided.*

In digitalis tinctures neither age, within reasonable limits, nor reaction influences materially the stability, although the effect of age on deterioration must probably be taken into account with the aqueous solutions.[9]

All of the factors necessary for a reliable product are readily controllable, and the conclusion seems inevitable that the fault lies with the

*The following note was received from Dr. Walter A. Jacobs, Member of the Rockefeller Institute for Medical Research, after he had reviewed the results of our experiments. Dr. Jacobs' work on the chemistry of the digitalis bodies has appeared over a period of years, chiefly in the *Journal of Biological Chemistry*. "I believe that there is no question that the deterioration of digitalis solutions is referable to the wide variation in P_H which has been found on examination of these solutions. We now know that the strophanthin and the digitalis bodies are very closely related substances. They possess in common certain chemical groups which make them more or less susceptible to acids or alkali. The latter produces definite chemical alterations in these substances with consequent pharmacological deterioration. I am sure that the method of using a buffer, which you found so useful in preserving solutions of ouabain, should be similarly applicable to other strophanthins as well as the digitalis glucosides and extracts."

TABLE III

HYDROGEN-ION CONCENTRATION OF COMMERCIAL PREPARATIONS OF DIGITALIS MARKETED IN GLASS AMPULES*

(Each figure given represents the average of determinations made on the contents of each of three ampules)

PREPARATION	P_H
Digifoline (Ciba)	5.4 †
Digalen (Roche)	6.4 †
Digitalin (Burroughs-Wellcome)	6.0 †
Digitos (Mulford)	8.0 †
Digitan (Merck) Lot No. 32840	7.47‡
Digitan (Merck) Lot No. 30521	7.70‡

*We are indebted to Dr. R. F. Loeb for these determinations.
†Colorimetric method.
‡Determined by quinhydrone electrode.

commercial drug houses. A pertinent example is furnished by experience with Digalen, manufactured by Hoffmann-LaRoche, Inc. This preparation was omitted from *New and Non-Official Remedies* by the Council on Pharmacy and Chemistry of the American Medical Association in 1914, because of misleading advertising claims and because of "quantitative differences in activity to the extent that some specimens examined were more than twice as active as others."[11] It is of interest to find that some of the figures then published by the Council, expressing the potency of various samples of Digalen (liquid) in terms of cat units (c.c. per kg.) are almost identical with those given in Table I (Lots 204169, 311030 and 311130). The 1914 figures are 1.52, 1.67, 1.73, 1.95, 2.03, 2.39, 2.50, 3.10 and 3.32. The newest Digalen liquid, in ampules (Lot 311191), standardized by the cat method by the manufacturer, showed in our laboratory a cat unit value of 71 per cent *greater* than its labeled biologic potency.

The results of our observations appear to indicate lack of adequate care on the part of the manufacturing drug firms in the preparation of digitalis products marketed in ampules. A sharp rebuke for misbranding the potency of a digitalis tablet was recently administered to one of these commercial houses.[12] A further lesson is evidently necessary. The situation calls for prompt remedial measures.*

SUMMARY

1. Different lots of five commercial preparations of digitalis, marketed in ampules, have been biologically assayed by the cat method of Hatcher and Brody.

*Our findings were communicated to the Medical Director of Hoffmann-LaRoche, Inc. In May, 1932, after this paper was submitted for publication, a letter was received from the Scientific Department of this company stating the following: (1) re-assay by the Roche Laboratories in Europe yielded a value which agreed with the original European assay; (2) the assay value of the ampule product, as determined by an American pharmacologist, as well as by the Referee on Digitalis of the Council on Pharmacy and Chemistry of the American Medical Association, agreed with that reported in this paper; (3) on the basis of these observations, the strength of Digalen solution has now been adjusted to correspond with the American assay, in terms of cat units; (4) all Digalen products sold in America will, in future, be assayed in this country.

2. Samples of all of the preparations so examined were found to be below the expected potency, as estimated in terms of a standard U. S. P. tincture. One lot of Digitan, however, was 97 per cent active. The newest preparation of Digalen, standardized by the manufacturer by the cat method, was 71 per cent stronger than its labeled biologic activity.

3. In four instances, different lots of the same product showed wide variations in potency.

4. Such variations in the strength of digitalis products marketed in ampules appear to indicate lack of adequate care on the part of the manufacturing drug firms in their preparation and labeling. The situation calls for prompt remedial measures.

5. Two specimens of commercial digitalis tincture were found to be fully potent. One sample was 28 per cent stronger than its labeled activity.

6. The one-hour frog method of digitalis assay, now official in the U. S. Pharmacopeia, has evidently not been found generally satisfactory for practical purposes, as evidenced by the continued use of cat, guinea pig and international units. It would be helpful both to the practitioners of medicine and to the drug manufacturers if a uniform standard were agreed upon and universally adopted in this country.

REFERENCES

1. Hatcher, R. A., and Brody, J. G.: The Biological Standardization of Drugs, Am. J. Pharm. **82**: 360, 1910.
2. The Second International Conference on the Biological Standardization of Certain Remedies, Pub. Health Rep. **41**: 505, 1926.
3. Wyckoff, J., Gold, H., and Travell, J. G.: The Importance of Differences in the Potency of Digitalis in Clinical Practice, AM. HEART J. **5**: 401, 1930.
4. Merck's Index, 4th ed., Merck and Co., Inc., 1930.
5. Sulzberger, M. B., and Mayer, R. L.: Sensitizations: Regional, Seasonal, Dietary and Other Influences Accounting for Variations and Fluctuations, Arch. Dermat. & Syph. **24**: 537, 1931.
6. Macht, D. I.: Influence of Barometric Changes on Potency of Digitalis for Cats, Am. J. Physiol. **97**: 540, 1931.
7. Behrens, B., Gros, O., and Hildebrandt, F.: Die Auswertung von Digitalispräparaten, München. med. Wchnschr. **78**: 2067, 1931.
8. Levy, R. L., and Cullen, G. E.: Deterioration of Crystalline Strophanthin in Aqueous Solution: Its Relation to Hydrogen Ion Concentration and a Method for Its Prevention, J. Exper. Med. **31**: 267, 1920.
9. Haag, H. A., and Hatcher, R. A.: The Stability of Digitalis and Its Preparations, J. A. M. A. **93**: 26, 1929.
10. Tainter, M. L.: The P_H and Potency of Digitalis Infusions, J. Am. Pharm. Assn. **15**: 255, 1926.
11. Report of the Council on Pharmacy and Chemistry, J. A. M. A. **63**: 881, 1914. Complete report published in reprint form by the American Medical Association, 1914.
12. Wyckoff, J., and Gold, H.: A Dangerous Preparation of Digitalis, J. A. M. A. **94**: 627, 1930.

MINIMAL TOXIC AND LETHAL DOSAGE OF DIGITALIS IN EXPERIMENTAL HYPER- AND HYPOTHYROIDISM*

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INTRODUCTION

THE tachycardia in clinical hyperthyroidism with or without auricular fibrillation and in the presence or absence of congestive heart failure does not usually respond to digitalis administration by slowing as well as it does in patients with a normal basal metabolic rate.[1] In view of this, experiments were planned in order to ascertain whether any difference existed in the amounts of digitalis necessary to cause toxic and lethal effects in normal, hyper- and hypothyroid rabbits.

METHOD

A modification of the Hatcher method[2] as used by Levine and Cunningham[3] was employed. The digitalis preparations were injected intravenously, by means of a small syringe, into the marginal ear veins of rabbits. The doses were divided and given at six-minute intervals. No anesthetic was used. It has been found that both the toxic and the lethal doses of digitalis are independent of the speed of administration of the drug in cats when the experiment is conducted within a period of from fifteen minutes to four hours[4] and that the effects from digitalis are lost more rapidly in rabbits than in cats.[5] Experiments of comparatively short duration were therefore thought advisable. For this reason the size of the doses was adjusted so that a lethal result would be obtained in about thirty to forty minutes in each experiment. The method was checked by the use of crystallized ouabain (Arnaud) in two experiments on normal rabbits. The minimal lethal doses found in these two normal rabbits agreed closely with those obtained by Hatcher.[5] Thereafter, a proprietary injectable tincture of digitalis (Digalen-Hoffman La Roche) was used.

TECHNIC

Electrocardiograms were taken from leads applied to the right foreleg and left hindleg of the animals. Tracings were made one minute before each injection and more often when toxic or lethal effects were being approached. After the experiment

*From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, and the Department of Medicine, Harvard Medical School.
This study was conducted in part under a grant from the Proctor Fund for the Study of Chronic Diseases.

was completed, the first appearance of ectopic beats in the tracing was taken as the earliest indication that the toxic dose had been administered.[4] Auscultation of the heart at frequent intervals often gave an indication that an electrocardiographic tracing should be taken between the usual six-minute intervals. The minimal lethal dose was that amount of the drug which just caused standstill of the heart and death.[2]

Twenty-one rabbits were used. Eight were made "hyperthyroid"; of these, six received one mg. thyroxin (Squibb) subcutaneously each day for three days, and two were fed 0.260 gm. (gr. iv) dessiccated thyroid gland (Armour) daily for three weeks. In each instance the basal metabolic rate became definitely elevated and ranged from +45 per cent to +90 per cent, averaging +54.6 per cent above the normal level. Three of the animals were thyroidectomized and their basal metabolic rates determined at frequent intervals until in each case the rate fell to −30 per cent or lower. The average basal metabolic rate of this group of hypothyroid rabbits was −32.5 per cent. Ten normal rabbits were used as controls. The basal metabolic rate of these animals was determined in most cases and was always within normal limits.

The oxygen consumption was determined by means of a Benedict portable respiration apparatus[6] connected to a water-sealed animal chamber, using an outside electric motor blower. Wilson's soda lime was used for the absorption of carbon dioxide. The animals were fasted at least eighteen hours before each test. Successive ten-minute periods of measured oxygen consumption were run until three consecutive checks were obtained.

RESULTS

There was a striking lack of difference in the cardiac response of the animals in the three groups to the action of digitalis (Table I). The average minimal toxic dose varied from 196 to 213 mg. per kg. The average minimal lethal dose was likewise almost constant, ranging in the three groups from 318 to 324 mg. per kg. The percentage of the minimal lethal dose which was toxic varied from 60.8 per cent to 65.3 per cent. This is in agreement with the observations of other workers who used only normal animals.[3, 4, 7] It is evident that the toxic and lethal doses of digitalis were not altered by the changed metabolism of the hyper- and hypothyroid animals.

Hatcher found that the fatal dose of digitalis in normal rabbits weighing 1800 gm. or less to be from 200-250 mg. per kg.[5] In our experiments the average minimal lethal dose in normal rabbits averaging 1940 gm. in weight was 318 mg. per kg., and the average minimal lethal dose in the three groups of animals was 320 mg. per kg. The weights of the animals in these groups averaged 2180 gm. A preliminary check of the

TABLE I

THE MINIMAL TOXIC AND MINIMAL LETHAL DOSES OF DIGITALIS IN MG. PER KG. IN NORMAL HYPER- AND HYPOTHYROID RABBITS

GROUPS	NO. ANIMALS	AV. BMR%	AV. MTD MG/KG	AV. MLD MG/KG	MTD —% MLD
Normal	10	±0	203	318	63.8
Hyperthyroid	8	+54.6	196	322	60.8
Hypothyroid	3	−32.5	213	324	65.3

method with ouabain had yielded results almost exactly similar to those obtained by Hatcher with ouabain in rabbits. The fact that our minimal lethal dose of digitalis was higher than that reported by Hatcher was due, apparently, to lower potency of the digitalis preparation which we used.

In all the rabbits except three the earliest sign of digitalis toxicity was the appearance of ectopic ventricular beats in the electrocardiogram. In two of the three exceptions premature auricular beats appeared first; in the remaining animal the first electrocardiographic abnormality to appear was a change in the character of the QRS complex. This may be considered an evidence of digitalis intoxication.[3] The three animals mentioned above died of digitalis poisoning without showing curves typical of ventricular extrasystoles.

No constant effect on the character of the T-wave was observed in the animals.[8, 9] There was one instance of flattening and one of inversion of the T-wave, and in another single case the T-wave became inconstant in shape after the toxic dose had been reached. These changes took place shortly before death. The T-waves remained unaffected in the remainder of the cases.

The commonest cardiac arrhythmia just prior to death was multiple ventricular ectopic beats. There were occasional instances of auricular fibrillation, auriculoventricular dissociation, paroxysmal ventricular tachycardia and ventricular fibrillation. Electrocardiographic tracings in many cases were not continued until final cardiac standstill occurred.

CONCLUSION

Hyperthyroidism was produced in eight rabbits, and hypothyroidism in three rabbits. It was found that the minimal toxic and minimal lethal doses of digitalis in these two groups were not significantly different from those in normal animals.

REFERENCES

1. White, P. D.: Heart Disease, p. 385, New York, 1931, The Macmillan Co.
2. Hatcher, R. A., and Brody, J. G.: A Biological Standardization of Drugs, Am. J. Pharm. **82**: 360, 1910.
3. Levine, S. A., and Cunningham, T. D.: Margin of Safety of Intravenous Digitalis in Cats, Arch. Int. Med. **26**: 293, 1920.
4. Levine, S. A.: The Action of Strophanthin on the Living Cat's Heart, J. Exper. Med. **29**: 485, 1919.
5. Hatcher, R. A.: Persistence of Action of the Digitalins, Arch. Int. Med. **10**: 268, 1912.
6. Benedict, F. G.: A Portable Respiration Apparatus for Clinical Use, Boston M. & S. J. **178**: 667, 1918.
7. Halsey, J. T.: The Digitalized Dog's Heart, J. Exper. Med. **25**: 729, 1917.
8. Blumenfeldt, E., and Strauss, S. G.: The Effect of Digitalis on the Final Deflection of the Electrocardiogram, Ztschr. f. klin. Med. **113**: 502, 1930.
9. Brams, W. A.: The Effect of Digitalis on the Electrocardiogram, Arch. Int. Med. **43**: 676, 1929.

OBSERVATIONS ON ELECTROCARDIOGRAPHY IN HEART DISEASE ASSOCIATED WITH PREGNANCY WITH ESPECIAL REFERENCE TO AXIS DEVIATION*

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PHYSICAL examination of the heart during the course of pregnancy not infrequently reveals signs which may suggest heart disease to the examiner. Tachycardia, systolic murmurs, usually at the base, less often at the apex, reduplicated sounds, or third heart sounds and accentuated apical first sounds are found which are sufficient to cause one out of nine pregnant women when first seen to be referred to the cardiac clinic at the Boston Lying-In Hospital for further study. These signs may or may not be accompanied by mild dyspnea on exertion, night starts, palpitation and sighing respiration, together with a doubtful or even a positive rheumatic history. Sometimes symptoms alone are grave enough to require special cardiac examination. In such cases, in addition to physical examination and x-ray study, one resorts to electrocardiography, especially for the estimation of the axis deviation as an aid in making a diagnosis or excluding the possibility of rheumatic valvular heart disease or congenital cardiac defect.

During pregnancy the special and variable condition under which the electrocardiographic examination is made results from the influence on the height of the diaphragm of the enlarging uterus or from the gradually increasing physiological load on the cardiovascular system and the organism generally. Jensen and Norgaard[1] studied the axis deviation as estimated by the relation between R_3 and S_3 in 239 normal pregnant women and found a tendency toward left axis deviation during the first months of pregnancy, and in the later months a return toward the right deviation. In their opinion this was independent of any change in position of the heart. They interpreted their findings as an early left ventricular hypertrophy followed by a later compensatory right ventricular hypertrophy. We have tabulated and averaged the axis deviation of 193 electrocardiograms on normal patients taken at various times during pregnancy and have found, as illustrated by Fig. 1, that the axis shifts to the left during the first two trimesters of pregnancy and tends to return to the right during the last trimester, the most definite shift to the right in our experience occurring between the eighth and ninth months. We suspect that this effect late in pregnancy may be due to the phenom-

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enon of "lightening" when the uterus assumes a somewhat lower position as it commonly does when the head engages during the last weeks of pregnancy in primiparae. A similar effect in multiparae results from the more pendulous abdomen late in pregnancy when the uterus and its contents fall forward with consequent release of upward pressure on the diaphragm. Not infrequently both normal women and women with organic heart disease experience amelioration of dyspnea at this time. Whether one interprets this shift in the electrical axis of the heart as

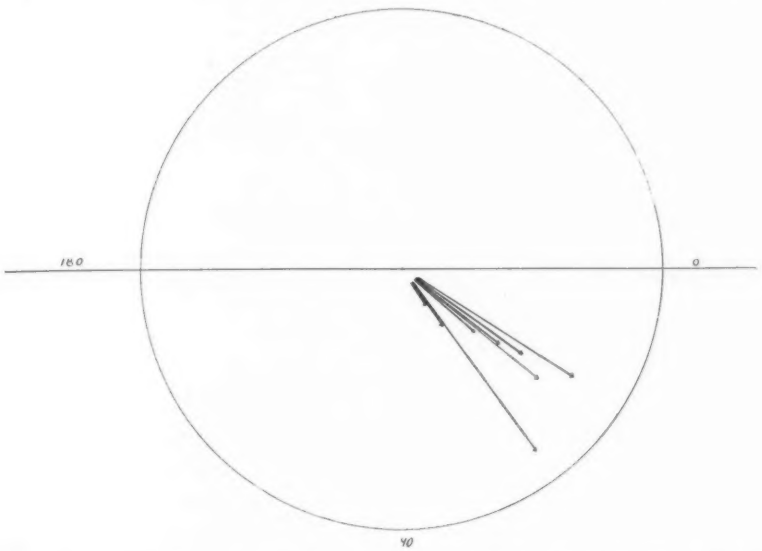

Fig. 1.—Arrows represent the average electrical axis of the heart determined from 193 electrocardiograms on normal patients at different months of pregnancy from the second through the ninth. The length of the arrow indicates the month from the shortest, second month, to the longest, ninth month. The distribution of the cases and the average angle found were as follows:

MONTH OF PREGNANCY	NO. OF ELECTROCARDIOGRAMS	AVERAGE ANGLE
2	5	56
3	15	54
4	20	40
5	38	37
6	33	35
7	41	38
8	29	32
9	12	53

It appears that the electrical axis tends to shift toward the left during the first two trimesters of pregnancy and to return toward the right during the third trimester.

first a left and then a compensatory right ventricular hypertrophy as do Jensen and Norgaard,[1] or as due to changes in position of the heart which are mechanical in nature as we are inclined to suspect, *it is nevertheless clear from our findings that there is a definite progressive tendency toward left axis deviation in the electrocardiogram from the second to the sixth month, while the axis remains about the same in the seventh and eighth months, definitely shifting back to the right in the ninth month.* A further shift to the right is commonly, though not always,

noted after parturition. This is shown in Fig. 2, which represents the electrical axis in four normal patients at the ninth month and after the puerperium. The shift was from twenty to thirty degrees to the right in three cases. There was no shift in the fourth case.

It is apparent from these considerations that the estimation of axis deviation probably will not be useful in the study of patients during pregnancy unless interpreted in the light of these results. This is illustrated by the electrocardiographic findings in forty-nine cases of

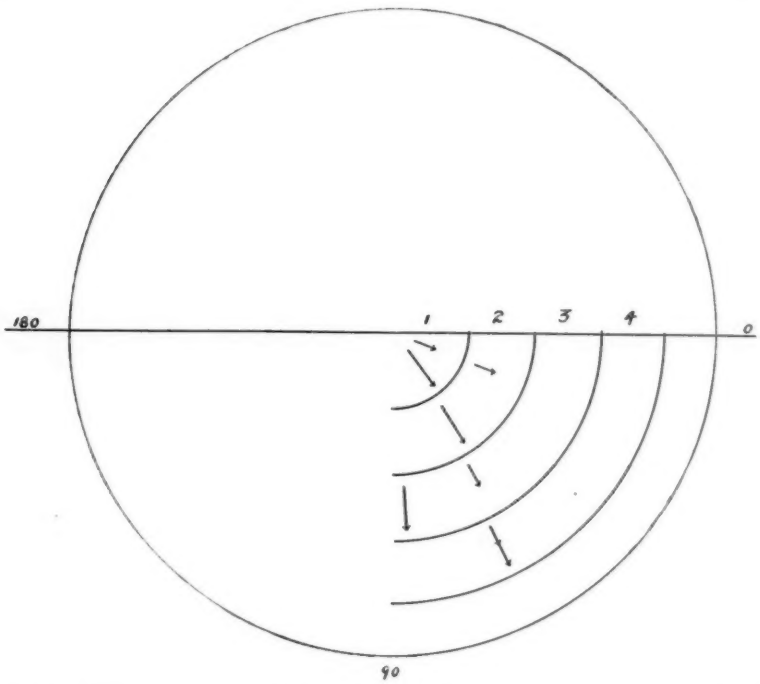

Fig. 2.—The electrical axis of the heart late in pregnancy and postpartum in four patients with normal hearts. The four patients may be summarized as follows:

PATIENT	AGE	PARITY		ELECTRICAL AXIS		ELECTRICAL AXIS
1	25	ii	9th mo.	20	6 wk. postpartum	52
2	21	i	9th mo.	20	2 wk. postpartum	56
3	27	iv	9th mo.	59	3 mo. postpartum	85
4	23	ii	9th mo.	62	2 mo. postpartum	62

The shorter arrow represents the angle at the ninth month of pregnancy and the longer arrow the angle found postpartum.

organic heart disease in pregnant women. Only thirteen showed abnormal axis deviation, considering 0 to 90° as the normal range. There were twenty-five cases of mitral stenosis of rheumatic origin. One showed right axis, three showed left axis deviation, and the remaining twenty-one were normal. There were nine cases of organic mitral regurgitation of rheumatic origin. One showed right axis deviation, four showed left axis deviation, four had normal axes. There were

twelve cases of aortic regurgitation. Nine had normal axes, three showed left axis deviation. There were three cases diagnosed as congenital heart disease. One of them showed right axis deviation. Two had normal axes. *It is apparent, therefore, that unless a sufficiently large number of normal pregnant women could be electrocardiographed each month during pregnancy so that the average shift of the heart could be accurately estimated and the Einthoven triangle rotated in the appropriate direction by an accurate average amount, the use of axis deviation as ordinarily interpreted for aid in the diagnosis of valvular disease or congenital defects during pregnancy is likely to be unsatisfactory.*

While reviewing our findings in regard to axis deviation we found twenty-nine, or slightly less than 11 per cent of 264 electrocardiograms showing complete inversion of Lead III. In about half of these cases the electrocardiogram was taken in the third trimester of pregnancy. The outcome of the pregnancy was good for both mother and baby in twenty-six of the patients on whom the electrocardiograms were taken, good for the mother while the baby was stillborn in one, and good for the mother in one case while one of twins was stillborn, and one was viable. The outcome was unknown in one patient delivered by her local doctor. Our conclusion was that this finding represented a transverse position of the heart and was not indicative of any organic change. This is in agreement with the findings of Bland and White.[2]

CONCLUSIONS

1. Electrocardiographic study for the estimation of axis deviation as an aid in the diagnosis of acquired valvular disease or congenital defects during pregnancy is unreliable since the axis tends to shift toward the left during the first two trimesters and to return toward the right during the third trimester and since accurate average corrections for this shift can not now be made.

2. Serial electrocardiograms throughout pregnancy on a sufficiently large number of normal women are required in order to determine accurately the variable limits of axis deviation during pregnancy.

3. Inverted Lead III is of no significance, probably being due to transverse position of the heart.

REFERENCES

1. Jensen, F. G., and Norgaard: Functional Cardiac Diseases and Essential Cardiac Hypertrophy in Normal Pregnant Women, Act. Obstet. et Gynec. Scand. **6**: 67, 1927.

2. Bland, E. F., and White, P. D.: The Clinical Significance of Complete Inversion of Lead III of the Human Electrocardiogram, AM. HEART J. **6**: 333, 1931.

NOTES ON HEART FAILURE

With Report of a Case of Pure Left Ventricular Failure*

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IN SPITE of the vast amount of work that has been done on the physiology of cardiac failure our knowledge of the subject is still largely empirical, and our drug therapy, satisfactory as it is in most instances, is none the less very far from being strictly scientific. By drawing upon the store of accumulated experience we are enabled to classify our cases after a fashion and to treat them more or less successfully, but until we encounter a refractory case we do not realize how often we are saved from therapeutic defeat by the fact that our sovereign remedy, the foxglove, is applicable to almost all varieties of heart failure. The fact is that we are as much at a loss to explain why digitalis usually succeeds as we are to understand why it occasionally fails. We are told that digitalis decreases the cardiac output in normal men and dogs,[1, 2, 3, 4] but increases it in cardiac failure,[5]† which would be no less convincing if it were less paradoxical. The validity of the old assumption that heart failure always means diminished cardiac output has recently been questioned seriously. As Wenckebach[7] says, there is almost an oppressive unanimity in the statements coming from all sides that under certain circumstances the cardiac output may be normal or actually increased. If this be true, is the effect of digitalis on cardiac output in heart failure invariably the same, or does it vary, and what determines its mode of action?

Our clinical experience with the mercurial diuretics has taught us that there must be peripheral, as well as cardiac, factors in what we call "heart failure," and the work of Eppinger, Kisch and Schwarz,[8] and Harrison and Pilcher,[6, 9] to mention but a few, has shown that such is actually the case. The effect of edema on the utilization of oxygen by the tissues and on minute-volume blood flow, incomplete resynthesis of glycogen into lactic acid by the skeletal muscles, with all the ensuing metabolic disturbances, and variations of the circulating and noncirculating blood volume, are some of the peripheral factors which must be taken into account. The idea that heart failure cannot be explained on a simple hydraulic basis is not new.[10]

To assimilate the often contradictory experimental data and apply them successfully to the problem of untangling the snarl of cardiac, renal, vascular, lymphatic, respiratory and cytological factors in heart

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†The dissenting opinion of Harrison and Pilcher[6] is based on indirect evidence.

failure is a feat which surpasses even the ingenuity of Wenckebach.[7] The one thing which is needed, above all other things, to lead us out of this wilderness and start us on the road toward a rational understanding of heart failure is a sufficiently accurate, clinically applicable method of measuring cardiac output.[10, 11, 12]

The following case of pure left ventricular failure not only illustrates some of the difficulties which beset the clinician in his endeavor to analyze heart failure into its component physiological factors, but nearly epitomizes the entire problem.

CASE REPORT

History.—The patient was a physician, aged sixty-one years. His principal complaint was of air hunger, which he noticed for the first time in the early summer of 1931, while playing golf; the attack was not severe and did not last long. Thereafter on several occasions he felt a little short of breath at night, without any antecedent physical exertion, but the warning was so slight that he disregarded it. The first really alarming attack occurred in July, 1931, while the patient was touring in the East. One night after retiring he became so short of breath that he was compelled to sit up in bed, and for about an hour he suffered from a feeling of substernal tightness and inability to breathe. After the symptoms subsided he felt none the worse, and was able to resume his trip the next day.

One day in August, 1931, while the patient was reclining on the couch after luncheon, his left arm and leg suddenly became numb. There was no involvement of the face, or of speech, and he was able to rise and walk immediately, but subjective sensory disturbances persisted in the arm and leg for several days, and were attended with impairment of dexterity in the use of the hand. When he was examined a few days later his arterial pressure was found to be 215/138 mm. Hg, but no objective neurological signs were demonstrable. The patient did not know when his blood pressure first began to manifest an upward tendency. It had been measured once in 1930, at which time the systolic level stood at 180 mm. Hg, but beyond this no information was forthcoming. For some time he had been finding it necessary to get up once or twice each night to pass urine, and after his August experiences he began to examine his urine occasionally. He found that it usually contained a small amount of albumin and now and then a few hyalin casts.

By the latter part of November, 1931, the patient was noticing slight air hunger on exertion. At the hospital where he visited his patients he was content to wait for the elevator, instead of climbing the stairs as had been his custom. Later in December the attacks of subjective respiratory distress began to return, chiefly at night, and quite apart from physical exertion. Again the sensation was one of substernal constriction and inability to breathe. He had the feeling that he would obtain relief if he could bring up something from his lungs, which was true to a limited extent, but his efforts to raise sputum were seldom successful, and the amount was always very small. The sputum was never bloody. He found that he was more comfortable sitting up and leaning forward than in any other position. He had no pain anywhere at any time. The symptoms did not abate spontaneously, as on former occasions, but grew steadily worse, so much so that for a period of ten days prior to his admission to the University Hospital he had scarcely any repose, day or night. The feeling of tightness in his chest was always present, increasing at times to such an extent that he feared it would strangle him.

Physical Examination.—At first the patient seemed convinced that he was suffering from bronchial asthma; he had already been subjected to skin sensitization

tests, and wanted more. Asthma and emphysema were quickly ruled out, however, by demonstrating that the volume of the lungs was not increased to any significant extent, that râles of all kinds were conspicuous by their absence, and that the vital capacity, which measured 2300 c.c., tended rather to decrease than to increase after the administration of adrenalin. The extensibility of the lungs was considerably impaired, but percussion and auscultation failed to show any general modification of lung density.

Outwardly the patient seemed fairly calm, yet there was something arresting about his appearance and demeanor. His face was of a grayish hue, and wore an anxious, worried expression. He seemed unable to describe his feelings clearly. Although he insisted that he was short of breath, his breathing was quiet and shallow, and except for its somewhat increased rate might have passed for normal. He himself readily admitted that his intense subjective respiratory distress was out of all proportion to the objective evidence thereof, and explained more exactly by saying that his breathing seemed in imminent danger of being choked off by a terrible sensation of constriction in the chest. The symptoms were remittent to some extent. Occasionally during the day he was comparatively comfortable for hours at a time. Toward night his distress increased, and often underwent rapidly recurring variations in intensity. After breathing fairly comfortably for a minute or two, an anxious expression would begin to gather in his face, and the substernal constriction would increase slowly until it became almost intolerable. At this point his face wore a look of agony and he was gasping for breath. The symptoms would then subside gradually, only to return again a few minutes later. This sequence would be repeated many times. During his first forty-eight hours in the hospital the patient's discomfort increased steadily. The throttling of his chest was accompanied by such a vivid premonition of death that he sent for a clergyman.

Examination of the heart showed that the left ventricle was enlarged; it was not abnormally accessible, but the left border lay about midway between the anterior axillary and midaxillary lines, and the medial half of the left costal margin moved outward only about half as far as the right. There were no signs whatever of enlargement of the right ventricle or right auricle. The first heart sound was unchanged, and there were no endocardial murmurs. The volume and contour of the arterial pulse were normal. The arterial pressure measured 200/140 mm. Hg. The aorta did not seem particularly accessible, although with the head one could feel a distinct systolic impulse and diastolic impact, and the aortic second sound was definitely accentuated. At the first examination the aorta was somewhat neglected, but nevertheless two examiners looked for aortic murmurs and found none. The cardiac mechanism was normal.

There were no indications of stasis proximal to the right ventricle, i. e., the right auricle was not dilated, there was no engorgement of the cervical veins, the liver was neither swollen nor tender, and there was no clearly demonstrable edema or cyanosis. The hands and feet were warm, and all the accessible arteries, although very sclerotic, pulsated normally.

There were, on the other hand, definite evidences of circulatory stasis proximal to the left ventricle, in spite of the absence of moisture from the air passages of the lungs. The vital capacity, i. e., lung extensibility, was reduced 50 per cent, a small amount of fluid was present in both pleural sinuses, and the roentgenogram showed the heavy septal markings characteristic of intrapulmonic stasis (Fig. 1).

The ophthalmoscopic examination revealed pronounced arteriosclerosis, and in the left eye an arteriosclerotic retinitis characterized by powdery areas of degeneration, transudation, edema, and hemorrhage.

Laboratory Examination.—Certain aspects of the electrocardiogram suggested coronary disease. The urine on two occasions contained a trace of albumin. There

was no retention of nonprotein nitrogen, but renal resourcefulness was reduced 58 per cent as determined by the urea clearance method. The blood Wassermann and Kahn reactions were negative. There was no anemia.

Summary.—History of paroxysmal nocturnal cardiac dyspnea, moderate air hunger on exertion, cerebral hemorrhage, high blood pressure, nocturnal diuresis, and albuminuria. Presence of air hunger and dyspnea, high arterial pressure, enlargement of the left ventricle, evidences of stasis in the pulmonary circuit without stasis in the greater circulation, widespread arteriosclerosis including electrocardiographic indications of coronary sclerosis, and relative renal insufficiency.

Diagnoses.—Pure left ventricular heart failure, with interstitial pulmonary stasis, but without actual pulmonary edema. General arteriosclerosis, including the arch

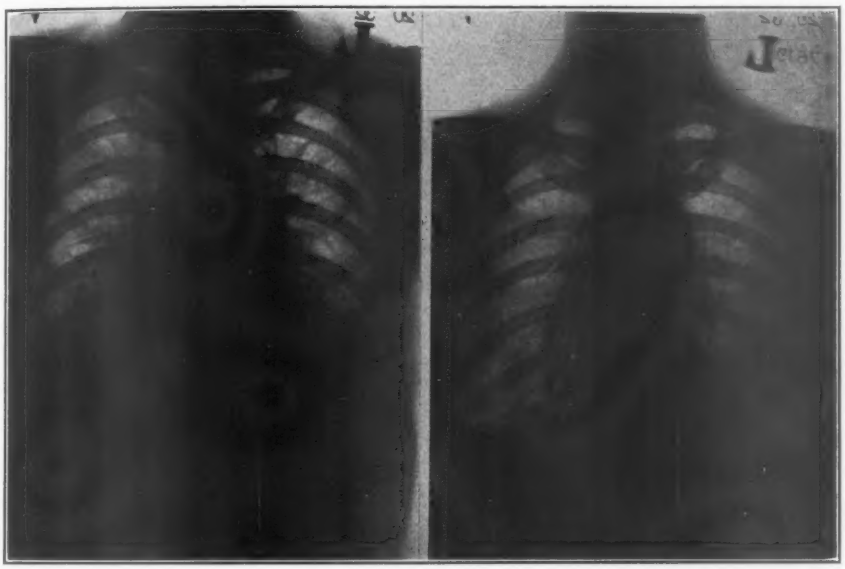

Fig. 1. Fig. 2.

Fig. 1.—First teleroentgenogram, showing the intrapulmonic stasis and bilateral pleural effusion. (Reproduction has somewhat exaggerated the original intensity and extent of the lung shadows.)

Fig. 2.—Second teleroentgenogram, five days later. The signs of intrapulmonic stasis have disappeared.

of the aorta, the coronary, retinal, and cerebral arteries, and arteriolar nephrosclerosis.

Subsequent Course.—No very satisfactory results followed the use of nitrites, epinephrine, morphine, or whiskey, although transient symptomatic improvement occurred once or twice. As soon as a rational diagnosis was made, 0.5 mg. of strophanthine was given intramuscularly, and on the following day the administration of digitalis leaves in doses of 0.1 gm. three times a day, and of euphyllin in doses of 0.2 gm. three times a day, was begun. Within a few hours after receiving the strophanthine the patient felt immensely relieved, and noticed the onset of profuse diuresis. Improvement continued steadily, and four days later the patient was a different man. All the agonizing sense of constriction of the chest and respiratory distress had disappeared, the ashen hue and anxious look were gone, there had been a weight loss of 5.5 pounds net, the vital capacity had risen from 2300 to 4000 c.c., the left ventricle was definitely smaller, and the pleural fluid and roentgenological

evidences of intrapulmonic stasis had vanished (Fig. 2). Incidentally, the arterial pressure had fallen to 170/120 mm. Hg.

The roentgenograms had shown elongation and dilatation of the aorta, and more careful examination just before the patient was discharged revealed all the usual indications of increased accessibility of its ascending and transverse portions, together with an aortic systolic murmur which had not been present at the first examination. This murmur can best be explained as the result of reduction in the diameter of the vestibular portion of the left ventricle consequent upon recovery from cardiectasis, the diameter of the aortic orifice and ascending aorta remaining unchanged throughout.

DISCUSSION

The most interesting features of this case were the behavior of the arterial pressure, the respiratory symptoms, the unusual character of the intrapulmonic stasis.

It might readily be assumed that high peripheral resistance was the primary cause of the left ventricular failure, and that interference with coronary blood flow acted as a contributory factor. Physiologists tell us (cf. Wiggers[13]) that when the heart is in prime condition it responds to increased resistance with increased initial and maximal tension and increased diastolic volume. The latter is a tonogenic, or physiological, dilatation. As a result the output of the ventricle remains the same, or even increases, and the duration of systole is actually shortened. This is the first phase of cardiac strain. The damaged heart responds in the same way, but soon passes into the second phase of strain, during which its inherent contractility suffers. The next stage is that of myogenic, or pathological, dilatation, characterized by diminished output. Failure begins when the heart receives more blood that it discharges. At this point stasis appears proximal to the ventricle, and systemic arterial pressure would fall considerably were it not for a "compensatory" vasoconstriction. Vasoconstriction occurring at this juncture could not possibly be genuinely compensatory, for it would create a vicious circle with the failing ventricle, besides producing peripheral disturbances. It is here that clinical experience and physiological predications part company. How can failure avoid growing progressively worse if the ventricle must continue opening the aortic valve against a very high diastolic pressure? How broad is the interjacent ground between moderate failure with stasis and sustained high arterial pressure on the one hand, and complete failure with falling pressure on the other? It is difficult to understand how patients can linger indefinitely in this intermediate state. Clinical experience does not confirm the dictum that arterial pressure always tends to fall as heart failure develops; cases such as this, in which the pressure remains very high in spite of desperate symptoms, are too common. If anything were needed to confuse matters further, it is furnished by the fact that as soon as recovery begins pressure falls, sometimes considerably below the pre-failure level, and one gains the impression that the fall is the result, rather than the cause, of recovery.

At least we are well rid of the old taboo against giving digitalis when arterial pressure is high.

If diminished cardiac output and secondary vasoconstriction are invariable consequences of left ventricular failure, why are there not plain evidences thereof, such as coldness and cyanosis of the hands and feet, and perhaps lowered pulse pressure? What is the relationship between heart failure and the temperature of the body surface? Other things being equal, why is it that some patients have cold hands and feet, whereas others exhibit extremities that are normally or even excessively warm?

A priori considerations suggest that pure unilateral heart failure, particularly of the left ventricle, should be rather common, but as a matter of fact it is rarely encountered except in the acute form which manifests itself as paroxysmal nocturnal cardiac dyspnea. It is characterized as a rule by relatively more severe respiratory symptoms than bilateral failure, the reasons for which are not clear in every case. The air hunger and dyspnea of the paroxysmal nocturnal seizures are generally proportional to the degree of intrapulmonic stasis and edema, and are regarded as the natural consequence of inability on the part of the left ventricle to handle the volume of blood which is being sent in normal quantities into the pulmonary circuit by the right ventricle. It is therefore to be inferred that the symptoms would be alleviated, at least partially, if the output of the right ventricle were to diminish. In the case here described, however, although the air hunger was moderately severe, it was no worse than it might have been in a comparable case of bilateral failure. The ventilatory capacity of the lungs was at all times adequate to the needs of the patient as long as he remained at rest. His shortness of breath was therefore not referable directly to impaired extensibility of the lungs, but presumably to vagus reflexes contingent upon diminished vital capacity.[14] Thus it is very unlikely that the supervention of right ventricular failure would have ameliorated his air hunger to any appreciable extent. On the other hand, the patient's terrible dyspnea, his acute sense of substernal constriction, and his vivid premonition of death were not only out of all proportion to his air hunger, but were far more intense than would be expected in bilateral heart failure of comparable degree. This conjunction of extreme dyspnea with relatively mild air hunger in pure left ventricular failure was one of the most noteworthy and most inexplicable features of the case. Whenever a critical analysis of respiratory symptomatology is attempted, it is imperative to distinguish sharply between air hunger and dyspnea. Morawitz and Siebeck[15] called attention to this fact in 1909, and it has been reemphasized repeatedly. No better example could be adduced than the case under discussion.

In any case of heart failure it is impossible to apprehend fully the part played by the left ventricle without spirometric estimation of the

vital capacity to determine the extent to which lung extensibility has been reduced by stasis in the pulmonary circuit. This is especially true in a case such as this, in which the stasis remained confined to the interstitial tissues. How pulmonary stasis can be purely interstitial, besides being extensive enough to reduce lung extensibility 50 per cent and produce air hunger and severe dyspnea without at the same time interfering with transpiration of gases across the alveolar membrane to the extent of inducing pronounced hyperpnea and cyanosis, is a mystery.

Further progress toward answering such questions as have been expressed or implied in this discussion awaits the introduction of a satisfactory method of measuring cardiac output in health and disease. Without such a method our knowledge of the physiology of heart failure stands at dead center, as did the physiology of diabetes before the discovery of insulin.

REFERENCES

1. Harrison and Leonard: The Effect of Digitalis on the Cardiac Output of Dogs and Its Bearing on the Action of the Drug in Heart Disease, J. Clin. Investigation **3**: 1, 1926.
2. Cohn and Stewart: Relations Between Cardiac Size and Cardiac Output Per Minute Following the Administration of Digitalis in Normal Dogs, J. Clin. Investigation **6**: 53, 1928.
3. Burwell, Neighbors and Regen: The Effect of Digitalis Upon the Output of the Heart in Normal Man, J. Clin. Investigation **5**: 12, 1927.
4. Stewart: Effect of Giving Digitalis on the Volume Output of the Heart and Its Size in Normal Individuals, Proc. Soc. Exper. Biol. & Med. **29**: 207, 1931.
5. Stewart: Effect of Giving Digitalis on the Volume Output of the Heart and Its Size in Heart Failure, Proc. Soc. Exper. Biol. & Med. **29**: 209, 1931.
6. Harrison and Pilcher: Studies in Congestive Heart Failure. I. The Effect of Edema on Oxygen Utilization, J. Clin. Investigation **8**: 259, 1930.
7. Wenckebach: Herz- und Kreislaufinsuffizienz, Medizinische Praxis, Band XII, Dresden, 1931, Theodor Steinkopff.
8. Eppinger, Kirsch and Schwarz: Das Versagen des Kreislaufes, Berlin, 1927, Julius Springer.
9. Harrison and Pilcher: Studies in Congestive Heart Failure. II. The Respiratory Exchange During and After Exercise, J. Clin. Investigation **8**: 291, 1930.
10. Hoover: General Considerations in Cardiovascular Disease, Osler's Modern Medicine **4**: 347, 1927, Philadelphia, Lea & Febiger.
11. Henderson: Volume Changes of the Heart, Physiol. Rev. **3**: 165, 1923.
12. Henderson and Haggard: The Circulation and Its Measurement, Am. J. Physiol. **73**: 193, 1925.
13. Wiggers: Modern Aspects of the Circulation in Health and Disease, Philadelphia, 1923, p. 561 ff., Lea & Febiger.
14. Harrison, Calhoun, Cullen, Wilkins and Pilcher: Studies in Congestive Heart Failure. XV. Reflex Versus Chemical Factors in the Production of Rapid Breathing, J. Clin. Investigation **11**: 133, 1932.
15. Morawitz and Siebeck: Die Dyspnoe durch Stenose der Luftwege. I. Gasanalytische Untersuchungen, Deutsches Arch. f. klin. Med. **97**: 201, 1909.

NOTE ON THE TRANSMISSION OF AORTIC SYSTOLIC MURMURS TO THE ABDOMINAL AORTA*

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SOME months ago while examining a patient with aortic stenosis, it was noted that the murmur was readily heard over the abdominal aorta in the region of the navel. Inasmuch as systolic murmurs in general are propagated best in the direction of the blood stream, the presence of the murmur is readily explained. However, several standard texts were consulted, and in none was there reference to the transmission of murmurs originating at the aortic valves or in the thoracic aorta to the abdominal aorta.

Notes have been collected on twenty-five patients. In eleven of these, a diagnosis of aortic stenosis was made. In nine, the murmur was transmitted to the abdominal aorta, while it was not heard there in two. In five cases of luetic aortitis with aortic insufficiency, having both systolic and diastolic murmurs at the aortic area, all showed transmission of the systolic murmur to the abdominal aorta. One patient with thoracic aneurysm without insufficiency and another with aortic insufficiency each had a systolic murmur over the abdominal aorta. One patient with arteriosclerosis and hypertension had a systolic murmur at the aortic area which was transmitted to the abdominal aorta. In one case of subacute bacterial endocarditis involving the aortic valve, with a to-and-fro murmur at the aortic area, a loud systolic murmur was audible over the abdominal aorta, much louder than that heard over the heart, suggesting the possibility of vegetations in the aorta. A patient with toxic adenoma of the thyroid with substernal extension of the goiter had a very faint systolic murmur audible at the aortic area. Immediately below the ensiform, the murmur was barely audible. It became much louder on approaching the navel and was faintly transmitted to the femoral arteries. The probable explanation of the murmur seemed to be the pressure of the very firm thyroid gland on the thoracic aorta. A patient with long standing adenoma of the thyroid developed malignant changes in the gland, which was largely intrathoracic. Signs of venous pressure were apparent. There were no murmurs over the precordium. A systolic murmur was audible above and below the navel over the aorta. X-ray films, as well as operative and postmortem findings, indicated that the thyroid gland was pressing on the thoracic aorta. A patient with thoracic aortic aneurysm came to autopsy. A murmur had been heard over the abdominal aorta but none over the aneurysm. In addition

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to aneurysm of the arch of the aorta, autopsy revealed atherosclerosis with calcification of the abdominal aorta, which may have contributed to the production of the murmur. Two patients with pernicious anemia, without demonstrable heart disease, had systolic murmurs, presumably "hemic," at the base of the heart. In each, the murmur was audible over the abdominal aorta, though very faint. The red cell counts were 1.5 and 1.2 millions, respectively.

The murmurs heard over the abdominal aorta have been noted in the region of the navel; usually about two fingerbreadths above and below it, and a little to the left of the midline. In most of the patients the murmur was heard best just above the navel. Generally, it was less intense or absent at some point between the navel and the ensiform. In one patient with aortic stenosis and in one with intrathoracic goiter, the murmur could be heard along the abdominal aorta, over the common iliac and femoral arteries. In one with luetic aortic insufficiency, a systolic murmur was heard over the aortic valve area, abdominal aorta and iliacs.

Compression of the aorta with the bell of the stethoscope must be avoided, though it is essential that the instrument be near the vessel. Failure to hear a murmur over the abdominal aorta in obese individuals may be due to the interposed layer of fat. In one patient with an aortic systolic murmur whose abdomen was distended and whose abdominal muscles were resistant, no murmur was heard; but when pressure was exerted with hands above and below the navel, the bell of the stethoscope was more nearly approximated to the aorta and a murmur was then audible. If one auscults over the femoral artery, one finds that considerable pressure is required to produce a murmur. In the average patient with abdomen of normal contour, it requires still greater pressure to produce a murmur over the aorta, and in our experience it is usually impossible to do this.

As a control, a series of 50 normal individuals has been examined. In none was a murmur audible over the abdominal aorta, and in only one, with very thin abdominal walls, was a murmur produced by pressure of the bell of the stethoscope. In examining patients with scaphoid abdomen, pressure with the bell of the stethoscope during auscultation over the aorta may produce a murmur and, therefore, must be avoided, since such a murmur has no diagnostic significance.

The intensity and quality of the cardiac murmur do not appear to be the sole factors which determine its transmission. When the abdominal aortic murmur is louder than that heard over the aortic valves, or when no thoracic murmur is detected, an extracardiac cause for the murmur, such as aneurysm, intrathoracic goiter or mediastinal neoplasm, should be looked for, in the absence of a demonstrable abdominal lesion.

A systolic thrill was found at the aortic area in association with the

murmur in many instances, particularly in aortic stenosis. But murmurs producing no palpable thrill are audible over the abdominal aorta quite as frequently as those associated with a thrill, so far as we can determine from this small series of cases.

These observations demonstrate that systolic aortic murmurs, regardless of their cause, are frequently transmitted from the aortic valves or thoracic aorta to the abdominal aorta. The finding of a murmur over the abdominal aorta is of no differential diagnostic value as to the type or etiology of a lesion of the aortic valves. In fact, a systolic murmur originating from a thoracic aneurysm or from external pressure on the thoracic aorta may be transmitted with the blood stream to the abdominal aorta. In some instances the murmur may not be detected over the thorax. In no case were diastolic cardiac murmurs heard over the abdominal aorta.

Systolic murmurs are frequently encountered in connection with aneurysm of the abdominal aorta. Any abdominal lesion causing pressure on the vessel and producing a relative stenosis may also cause a systolic murmur. The fact that similar murmurs may originate at the aortic valves or in the thoracic aorta should be kept in mind in connection with the diagnosis of abdominal lesions.

REFERENCES

Cabot, R. C.: Physical Diagnosis of Diseases of the Chest, New York, 1902, 2nd ed., Wm. Wood & Co.

Flint's Physical Diagnosis, 8th ed., by H. C. Thacher, Philadelphia, 1920, Lea & Febiger.

Norris, Geo. W., and Landis, H. R. M.: Diseases of the Chest, Philadelphia and London, 4th ed., 1929, W. B. Saunders Company.

Sahli, H.: Diagnostic Methods, Philadelphia, 1905, W. B. Saunders Co.

White, P. D.: Heart Disease, New York, 1931, The Macmillan Co.

OCCURRENCE OF SUBACUTE BACTERIAL ENDOCARDITIS IN MITRAL VALVULAR DISEASE WITH PREEXISTING AURICULAR FIBRILLATION*

A Case Report

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SOME years ago Libman[1] made the observation that patients suffering from chronic valvular disease with auricular fibrillation rarely developed subacute bacterial endocarditis. Subsequently he, Rothschild, and Sacks[2] studied the disturbances of cardiac mechanism in 123 cases of this disease. Auricular fibrillation was encountered only once during the active stage of the disease, and in that patient the rhythm had been normal until three days before death. Three other cases had already progressed to the bacteria-free stage. Their observations of patients with fibrillation convinced them that once this arrhythmia was permanently established, there was little danger of subacute bacterial endocarditis supervening. The observation that auricular fibrillation and active subacute bacterial endocarditis are mutually exclusive, save in an exceptional instance, they considered of diagnostic value.

Thayer,[3] in a series of fifty-two cases studied up to the fatal issue, noted auricular fibrillation in three instances. However, in one of the three, the arrhythmia appeared eight days before death. In the other cases no statement was made of the duration of this disorder of rhythm. Recently (1930) Thayer[4] stated that auricular fibrillation was noted in 5 per cent of a series of 100 cases of subacute streptococcal endocarditis studied until death.

Sprague[5] referred to one case in which auricular fibrillation had been present four years before the onset of the infection. The arrhythmia was abolished by the use of quinidine sulphate, but recurred six months before death at the time of the appearance of the infection.

Fulton and Levine[6] in their series of 111 cases, of which thirty were examined at necropsy, encountered auricular fibrillation only once and then as a terminal event.

Blumer[7] referred to 301 case records in which auricular flutter was encountered once, and auricular fibrillation four times. He noted that many of the records antedated the use of instruments suitable for accurately distinguishing arrhythmias.

Elsewhere we[8] have reported observations of two cases of subacute bacterial endocarditis showing many disturbances of the cardiac mech-

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anism. In one instance paroxysmal auricular flutter was recorded by electrocardiograms. While transitory disturbances of A-V conduction are not extremely rare, the occurrence of subacute bacterial endocarditis (Streptococcus viridans) in a patient with chronic rheumatic valvular disease and established auricular fibrillation is sufficiently unusual to warrant study of the following case.

CASE REPORT

The patient, I. G., was first enrolled in the Third (N. Y. U.) Medical Division Cardiac Clinic on November 1, 1929. She was twenty-four years old, a widow, and mother of four children. Her chief complaints were dyspnea and fatigue, cough, with occasional hemoptysis. epistaxis, palpitation, and slight precordial pain, all of about one year's duration. She had noticed slight swelling of her ankles since 1923. Recently she had occasional vertigo and "spells of feeling faint." In her past history she stated that she had had typhoid fever and pneumonia at four years, scarlet fever and tonsillitis at five years, measles and diphtheria at six years, whooping cough at nine years, and influenza at fourteen years. Heart disease was first discovered by a physician sometime between 1909 and 1913. Her family history is of interest because both her father and a brother died of heart disease, the former at fifty-three years, the latter at nineteen years.

On admission to the clinic in 1929, physical examination showed the patient to be well developed, obese, and neither dyspneic nor cyanotic. No subcutaneous nodules or petechiae were discovered. Pupillary reactions were normal. Examination of the heart revealed the maximum apical impulse in the fifth left intercostal space outside the midclavicular line. The sounds were of fair quality. There were a harsh, blowing systolic murmur and a rumbling, diastolic murmur accompanied by a diastolic thrill at the apex. A soft systolic murmur was heard at the base. P_2 was greater than A_2. The rhythm was totally irregular. The ventricular rate was 77, the pulse rate was 68. The blood pressure was 116/76 mm. The lungs were clear; liver and spleen were not palpable. There was no edema or clubbing of the fingers. Electrocardiograms showed auricular fibrillation. A teleroentgenogram showed an enlarged heart with accentuation of all the cardiac curves, especially the pulmonary artery and left auricular curves. Wassermann test was negative. The urine examination was negative, except for a trace of albumin.

The patient was digitalized and given a daily maintenance dose of 3 grains of digitalis (whole leaf). She attended the clinic about once a month. Auricular fibrillation persisted. The temperature ranged between 99° and 100.2°. Several months later she developed pain in the left shoulder which was intermittent during the next six months. At times the patient felt better, but she was never free of symptoms or fever. In December, 1930, the patient developed cough with grippe-like symptoms which gradually subsided, but reappeared in March, 1931. In May, 1931, arthritis of an ankle joint developed and was followed by involvement of the fingers of one hand. She gradually became worse, developed dyspnea at rest, cough and fever (101.4°) and complained of pain in the left shoulder and right ankle. At this time it was noticed that her complexion had changed, having become pale and pasty. Edema of the legs appeared. On her visit to the clinic on June 19, 1931, she complained of dizziness, fever, and pain in the extremities. The spleen was palpable. The ventricular rate was 100; pulse rate, 86. The patient was referred to the hospital that evening.

Admission to the Hospital.—The patient entered the hospital on June 24, 1931. On admission she complained of aching pain in the right shoulder, elbow, and right wrist joints, fever at night, dyspnea, and fatigue. Physical examination revealed

orthopnea of choice, moderate pallor, slight cyanosis of the lips and finger nails. Her fingers appeared to show slight clubbing (the patient herself said that they were formerly more tapered). The mucous membranes were pale and no petechiae were visible. The fundi showed no changes. Veins of the neck were not dilated. The lungs were clear. Examination of the heart revealed essentially the same findings as noted in the clinic. The rhythm was still totally irregular. The liver was palpable; the spleen was easily palpated and was tender. There were no signs of ascites. The extremities showed no edema. On the thenar eminence of the right hand there were two bluish spots which were not tender. The admission diagnosis was as follows: Cardiac*—(a) Unknown (rheumatic?) inactive and active (possibly subacute bacterial endocarditis), (b) enlarged heart, mitral stenosis, mitral insufficiency (possibly bacterial endocarditis), (c) auricular fibrillation, (d) Class III. Accompanying this diagnosis was a note written by the house physician, Dr. Marshall Brown, which we quote verbatim, "The fact that the patient has auricular fibrillation is against the diagnosis of bacterial endocarditis, but the marked anemia, fever of six weeks' standing, palpable spleen, and questionable petechiae on the right hand make this diagnosis one to be considered."

Subsequent Observations and Course in the Hospital.—Examination by one of us later revealed essentially the same findings. Pallor was marked although not of typical "cafe au lait" color. Petechiae were visible in the mucous membrane of the left cheek, and a small tender red area was found on the tip of the middle finger of the left hand (Osler node). The diagnosis offered was the same as that just mentioned except that we felt more certain of the presence of subacute bacterial endocarditis. A blood culture taken on June 25 was positive for Streptococcus viridans. On July 3, the patient experienced a sharp, agonizing pain in the left upper quadrant of the abdomen which did not radiate. Examination of the abdomen revealed marked rigidity, pain and tenderness over this area. There were no accompanying urinary symptoms. Splenic infarction was added to the diagnosis. Another blood culture, taken on June 30, showed numerous colonies of Streptococcus viridans.

Laboratory Data: 3,410,000 red blood cells; hemoglobin, 70 per cent; 7,600 white blood cells with 80 per cent polynuclears and 20 per cent lymphocytes. Blood Wassermann was negative; blood N. P. N. 34 mg. per cent; sugar, 115 mg. per cent; creat. 1.5 mg. per cent. All electrocardiograms showed auricular fibrillation. A urine sediment count (Addis)† was done with the following results: twelve hour vol. 296 c.c.; specific gravity, 1011; P_H 5.8, albumin negative; red blood cells 1,480,000; white blood cells, 5,032,000; casts, 79,900.

The patient grew progressively weaker, more anemic, and lost weight continuously. A third blood culture was also positive for Streptococcus viridans. On July 13 the patient insisted upon going home, leaving the hospital at her own risk. She was readmitted two weeks later, to another medical service, complaining of palpitation, weakness, fainting spells, chills and fever. From this time to death on August 6, the patient ran a downhill course, the outstanding feature of which was the increasing evidence of sepsis. The temperature fluctuated daily between 99° and 104° (F). There were no new physical findings. Final clinical diagnosis was: Cardiac—(a) Unknown (rheumatic fever?) inactive, bacterial endocarditis, Streptococcus viridans; (b) enlarged heart, mitral stenosis and insufficiency, bacterial endocarditis of mitral valve; (c) auricular fibrillation; (d) Class III. II. Focal embolic glomerulonephritis. III. Splenic infarction.

Necropsy Report.—The following is a résumé of the significant pathological find-

*Cardiac diagnosis conforms to the nomenclature recommended by the American Heart Association.

†Normal values for twelve-hour specimens should not exceed: red blood cells 500,000; white blood cells, 1,000,000; and casts up to 5000.

ings. The skin had a sallow tint. Two pinpoint, brownish spots resembling old petechial hemorrhages were found on the dorsum of the left hand. Another was seen at the base of the right thumb. In the conjunctival sac of the right eye, there was a linear brownish area on the temporal side about 4 mm. in length. The ankles presented a moderate degree of pitting edema. The peritoneal cavity contained no fluid. The left pleural cavity contained about 500 c.c. of clear amber fluid, and about 300 c.c. of similar fluid were found in the right pleural sac.

Heart.—On opening the pericardium, firm bands of fibrous tissue were found irregularly distributed and binding the parietal and visceral pericardium. The heart

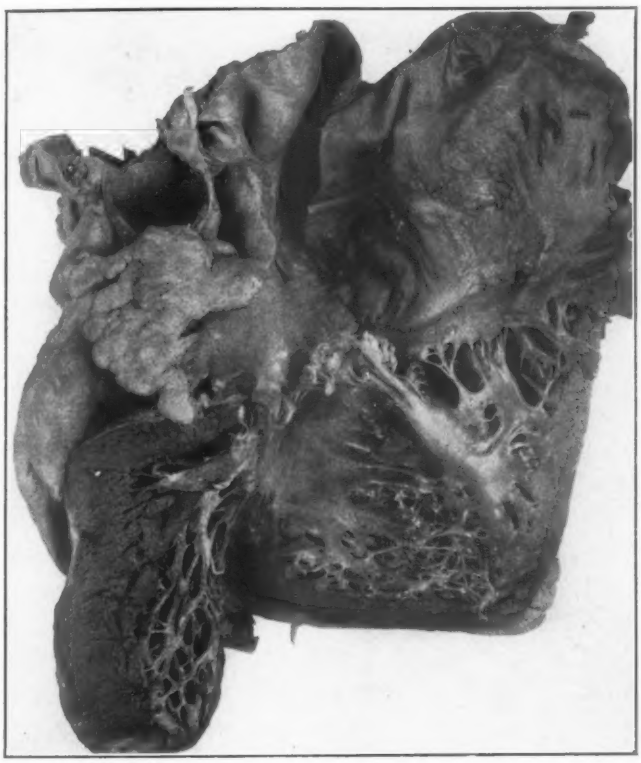

Fig. 1.—Photograph of heart to show marked dilatation of the left auricle, mural endocarditis of the left auricle and the old and recent lesions of the mitral valve.

weighed 470 gm. It presented marked dilatation of the left auricle. The right auricle appeared to be intact. The leaflets of the tricuspid valve were thin, translucent, and their chordae tendineae were delicate and shortened. The right ventricle showed slight hypertrophy. The pulmonary valves showed no naked eye changes. On opening the left auricle, it was found to be enormously dilated. (Fig. 1.) Its walls were thickened and on the lateral wall was seen a medallion-shaped patch, 4 by 5 cm., raised above the adjacent endocardium for a distance of 1 to 2 mm. Its surface was puckered, wrinkled, and composed of firm, pinhead sized verrucae. The auricular appendage appeared normal. The mitral orifice was stenotic, admitting two fingers. The valve showed marked thickening and fusion of the chordae tendineae, which were also shortened. The attached papillary muscles were notably hypertrophied. The aortic cusp of the mitral valve was the seat of a vegetative process

in which firm thrombotic material extended over both surfaces of the valve, and pedunculated vegetations reached into the ventricular chamber (Fig. 1). On the posterior cusp, a few thrombotic vegetations were also found. In addition, several small verrucae were noted. The vegetations appeared to be fairly well organized and were not friable. In the aortic leaflet calcific material could be palpated. The left ventricle showed moderate hypertrophy. The aortic valve was the seat of thrombotic vegetations which were found chiefly over the corpora arantii. These vegetations were small, polypoid, fairly firm, and quite irregular in shape. There was a slight degree of fusion in the commissure between the right coronary cusp and the non-coronary cusp. The coronary arteries appeared to be well preserved. The heart

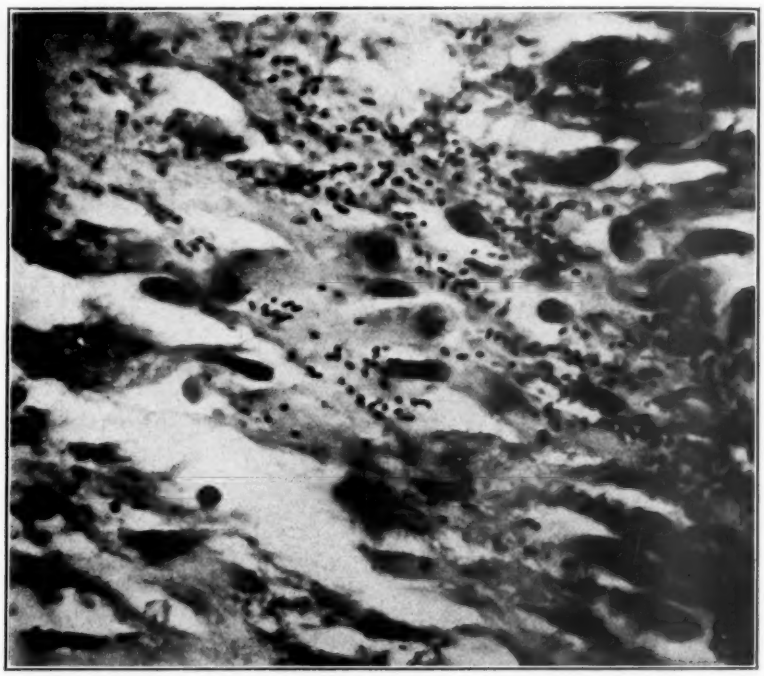

Fig. 2.—Photomicrograph (x1000) to show cocci in the depths of the vegetation on the aortic leaflet of the mitral valve.

muscle on section was pale, brownish red, and somewhat flabby. The aorta and pulmonary arteries were well preserved and showed only focal atheroma.

Lungs.—Except for bilateral adhesive pleuritis and moderate congestion and edema, no noteworthy abnormalities were noted. *Spleen:* In the spleen, which measured $18 \times 8 \times 8$ cm., there was found a cystic infarct, occupying the lower one-third of the organ. The cut surface was mottled green and purple, and revealed several infarcted areas. The lower pole was converted into a large necrotic cavity filled with homogeneous, foul-smelling, brownish material. *Liver:* Was enlarged and showed the markings of chronic passive hyperemia. *Kidneys:* Both kidneys were slightly enlarged and showed numerous anemic infarcts, chiefly cortical in distribution. No petechiae were noted. The other organs showed no especially significant changes.

Microscopic Report.—Heart and great vessels: Section through the wall of the left auricle showed marked thickening of the endocardium and numerous focal areas of cellular infiltration between the endocardium and the underlying auricular muscle.

A section through the area of endocarditis in the left auricle showed verruca formation. Sections of the mitral valve showed an ancient valvulitis with deposition of fibrous tissue which had become hyalinized. Blood channels were very numerous and arterioles showed advanced sclerosis. Sections through the vegetations showed infiltration by cells of all types, but chiefly histiocytic cells which extended freely into the thrombotic vegetations. Evidence of organization was seen in the infiltration by fibroblasts into the deeper parts of the thrombi. Gram-positive cocci were demonstrable in the sections through the vegetations on the aortic leaflet of the mitral valve (Fig. 2); none were seen in the sections through the posterior cusp or in the auricular lesion. Sections of the aortic valve showed sclerotic changes in the base and the free margin of the valve, suggesting previous mild focal inflammation. A section through the vegetation showed it to consist chiefly of fibrin with an inflammatory base composed of edematous collagen fibers and histiocytes, a few polynuclear leucocytes, and a few lymphocytes. Gram-positive cocci were demonstrated in the superficial layers of the vegetation. Sections of the other valves showed no inflammatory changes. Sections of the aorta and pulmonary artery were negative. Sections of the myocardium showed occasional areas of perivascular fibrosis. Occasionally intrafascicular scarring was encountered, but it was not marked except in the sections of the papillary muscles. No Aschoff nodules were found.

Kidneys.—Sections of both organs taken from areas adjacent to infarcts showed severe tubular degeneration with complete loss of nuclei, many tubular hemorrhages and much desquamated material in the tubular lumina. The glomeruli were so altered by the diffuse infarction that differentiation of embolic lesions was impossible. No bacterial masses were encountered.

Examination of the other organs confirmed the naked eye diagnosis.

Final Pathological Diagnosis.—Heart: Hypertrophy and dilatation; bacterial vegetative endocarditis (Streptococcus viridans), mitral and aortic valves; chronic valvulitis of mitral valve; mitral stenosis and insufficiency, verrucous thromboendocarditis of left auricle; chronic adhesive pericarditis; fibrosis of myocardium. *Spleen:* Multiple infarction with necrosis. *Kidneys:* Multiple bilateral infarctions. *Liver:* Chronic passive hyperemia. *Lungs:* Chronic passive hyperemia; edema; chronic adhesive pleuritis, bilateral.

COMMENT

Certain facts of clinical interest observed in this patient's course are worthy of emphasis. Thus we have proof of the existence of established auricular fibrillation for twenty-one months prior to death. From the patient's history a clue to the possible previous existence of this rhythm is found in her complaint of palpitation which began one year prior to entrance in the cardiac clinic.

It might be argued that bacterial endocarditis was present in this patient when her symptoms brought her to the cardiac clinic. Against this interpretation are the negative findings noted especially in her clinic visits: no splenomegaly, no petechiae, no clubbing of the fingers, no change in complexion, and no subjective complaint of fever until a new set of symptoms appeared in December, 1930, nine months before death. At this time "grippal" symptoms appeared, slowly subsided, and reappeared in March, 1931, five months before death. With the recrudescence of symptoms of weakness, fleeting joint pains, fever, increased fatigability, and the appearance of pallor, her clinical picture

took on a new aspect. Thereafter we find the development of all the confirmatory signs necessary to establish the diagnosis of subacute bacterial endocarditis. From this analysis the conclusion seems reasonable that auricular fibrillation was present for a considerable period (at least one year) before the onset of the terminal infective process.

The question of relationship between the occurrence of subacute bacterial endocarditis and advanced mitral stenosis has recently been studied by Sprague[5] and Fulton and Levine.[6] These observers agree that subacute bacterial endocarditis is rarely encountered in patients with advanced mitral stenosis. The case here presented showed signs of mitral stenosis and insufficiency in life. At necropsy the mitral valve measured 10 cm. in circumference at its base. It was rigid and the orifice was definitely, though *moderately*, stenotic. The shortened, thickened, fused chordae tendineae gave evidence of incompetency as well. The vegetations were hardly large enough to add to the degree of stenosis.

Thus in accord with the observations mentioned this patient did not have *advanced* mitral stenosis, although such might have been anticipated because of preexisting auricular fibrillation. It is interesting in this connection to note that in Sprague's cases the one patient with auricular fibrillation also had a wide mitral valve orifice, measuring 15 cm. in circumference. Any parallelism which might be drawn from the infrequency of the association of subacute bacterial endocarditis and advanced mitral stenosis on the one hand and auricular fibrillation on the other would have to take into account the frequency of auricular fibrillation in the various grades of mitral stenosis.

SUMMARY

A case of subacute bacterial (Streptococcus viridans) endocarditis is reported because of the occurrence of this disease in a patient with established auricular fibrillation associated with chronic rheumatic valvular disease.

REFERENCES

1. Libman, E.: The Clinical Features of Subacute Streptococcus (and Influenzal) Endocarditis in the Bacterial Stage, M. Clin. North America **2**: 117, 1918.
2. Rothschild, M. A., Sacks, B., and Libman, E.: The Disturbances of the Cardiac Mechanism in Rheumatic Fever and Subacute Bacterial Endocarditis, Am. Heart J. **2**: 356, 1927.
3. Thayer, William S.: Studies on Bacterial (Infective) Endocarditis, Johns Hopkins Hosp. Rep. **12**: 21, 1926.
4. Idem: Bacterial or Infective Endocarditis, Gibson Lectures for 1930, Edinburgh M. J. **38**: 237, 307, 1931.
5. Sprague, H. B.: Subacute Bacterial Endocarditis. A Correlation of the Clinical Evidence of Valvular Deformity With the Condition of the Valves as Found at Autopsy, J. A. M. A. **94**: 1037, 1931.
6. Fulton, M. N., and Levine, S. A.: Subacute Bacterial Endocarditis With Special Reference to the Valvular Lesion and Previous History, Am. J. M. Sc. **183**: 60, 1932.
7. Blumer, George E.: Subacute Bacterial Endocarditis, Medicine **2**: 105, 1923.
8. de la Chapelle, C. E., and Graef, I.: Two Unusual Cases of Subacute Bacterial Endocarditis (Streptococcus viridans), M. Clin. North America **14**: 1335, 1931.

EFFECT OF ASPHYXIA AND OF ANOXEMIA ON THE ELECTROCARDIOGRAM*

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THE changes in the electrocardiogram taking place during experimental asphyxia have been the subject of several investigations by different observers.[1, 2, 3, 4] The results of these observations are not, however, concordant. The clinical as well as experimental understanding of the effect of asphyxia on the electrocardiogram is of an obvious importance. A better knowledge of the effect of asphyxia on the electric potential of the heart would assist in separating many complex and hitherto obscure points of cardiac disease as recorded by the electrocardiogram. Particularly is this true clinically, as asphyxia and anoxemia are usually accompanying factors of heart disease.

The experiments described in the present communication were performed with the object of securing further information on this problem.

Before proceeding with a description of the methods used and of the results obtained it is necessary to define with somewhat greater precision the rather general term of asphyxia. Under asphyxia is understood a complex condition resulting (a) from an acute diminution of oxygen supply to an animal or one of its organs and simultaneously (b) from a diminished removal of the products of metabolism produced by the animal or organ. In other words asphyxia of an organ consists of a state of anoxemia complicated by an accumulation in the organ, i. e., in the blood perfusing it, of carbonic acid and lactic acid together with various other normal and abnormal products of metabolism. The method of the previous observers has been either to obstruct the blood flow through the coronary blood vessels[5] or to produce a general asphyxia of the whole animal.[6] In our experiments we endeavored to study the effect of asphyxia as well as of its component parts separately so as to determine which aspect of the asphyxial condition is chiefly responsible for the changes in the electrocardiogram.

All experiments of previous observers in this field have been done on the intact animal. It is obvious that in order to study the direct effect of asphyxia on the heart it is necessary to rule out all possible effects which asphyxia may exert on the heart indirectly, for instance through the central nervous system or by changing the blood pressure. The

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necessary control can only be achieved in experiments performed on the heart lung preparation.

All our experiments were performed on dogs from eight to ten kilograms in weight. The animal, after injection of a small dose of morphine, was anesthetized with chloroform and ether mixture, placed in position on the board, and its electrocardiogram was taken with standard leads before the beginning of the preparation. The heart-lung preparation was then made, and the electrocardiogram was retaken in order to determine whether it showed any changes as result of the operation and especially to determine the angle to which the heart became displaced by the manipulation; in the greater majority of experiments this was entirely negligible. All the experiments were performed at a constant arterial blood pressure and output of the heart. In most cases the arterial pressure was adjusted to 100 mm. Hg and the output to 600 c.c. per minute. Asphyxia of the whole heart was produced in the experiments either by shutting off the respiration or by restricting the blood supply to the heart muscle by severe coronary vasoconstriction following introduction of pitressin into the circulating blood. In some experiments asphyxia was produced by increasing the dead space of the respiratory system and making the animal rebreathe the same air.

Anoxemia of the whole heart was produced by administration of potassium cyanide, and excess of CO_2 by administering blood which had previously been exposed to a definite tension of carbonic acid. Local cardiac asphyxia was produced by temporary clamping of the coronary arteries, or by perfusing them with asphyxial blood removed from another heart lung preparation. In similar manner were also produced local anoxemia and excess of CO_2.

In prolonged experiments the electrocardiogram was taken at intervals of two minutes; in the case of administration of the quickly acting pitressin and cyanide the records were run continuously.

GENERAL CARDIAC ASPHYXIA

(a) By Arrest of Pulmonary Ventilation. After having taken several normal electrocardiograms the respiratory pump would be stopped and the heart-lung preparation was gradually asphyxiated. At a degree of asphyxia which corresponds to 50 per cent oxygen unsaturation of the blood, the heart starts to dilate and the blood pressure drops. The arterial blood pressure could be, however, easily adjusted by means of the variable resistance of the heart-lung apparatus. As asphyxia continues, this adjustment becomes more and more difficult and finally impossible. In some of our experiments asphyxia was carried to the stage at which the arterial blood pressure dropped to about 50 mm. Hg. The asphyxia was terminated either by switching in the respiratory pump or by administration of freshly oxygenated blood. Usually the recovery of the heart was rapid and complete, but in a certain number of cases where

the asphyxia was pushed too far the experiment ended by development of heart-block or of ventricular fibrillation.

The changes observed in the electrocardiogram in asphyxia of the heart lung preparation in the early stages were similar to those noted by one of us in the intact animal.[2] The usual observation was an elevation or a depression of the R-T interval above or below the isoelectric level of the electrocardiogram. The change in the R-T interval in the present series of experiments on the heart-lung preparation was not very conspicuous. In the early stages of asphyxia, up to the point of about 50 per cent oxygen saturation of the blood, there was usually a progressive diminution in size of the T-wave in all leads. Further deoxygenation of the blood, below 50 per cent, was accompanied by an inversion of the T-wave, usually in Lead I, although inversion of the T-wave in all three leads was not uncommon. At about the same time but sometimes only with further deoxygenation, down to about 25 per cent oxygen saturation, the change in the R-T interval of the electrocardiogram was noted, which progressed with the continuation of the asphyxia. The change consisted usually of a depression of the R-T interval in Lead I and an elevation in Lead III, although sometimes elevation in all leads or a depression in all leads occurred.

Asphyxia in its later stages caused the heart to slow from ten to fifteen beats per minute. This slowing was accompanied by a progressively increasing dilatation of the ventricles. The left side of the organ dilated more than the right during the early stages of asphyxia. An unmistakable dilatation of the left ventricle began with about 40 per cent oxygen saturation of the blood, and, at the time, the T-wave was found to be inverted in Lead I.

Resumption of the respiration or administration of fresh blood at any time before an extreme state of dilatation of the heart was reached caused a complete return of the electrocardiogram to normal. In some severe cases the recovery of the heart had to be assisted by massage.

(b) By Pitressin. The vasoconstrictor action of pituitary extract and of pitressin on the coronary blood vessels is very considerable, as has been shown by several previous observers. In fact it is so conspicuous that the organ shows signs of acute deprivation of oxygen and all the symptoms of cardiac asphyxia. In our experiments injection into the general circulation of the heart-lung preparation of 0.5 to 1.0 c.c. (P.D.) of pitressin had an effect very similar in character to that of asphyxia in regard to the general activity of the heart as well as the electrocardiogram. Slowing of the heart usually began forty seconds after injection of the drug and reached its maximum at about seventy seconds when the heart slowed by 10 to 15 beats per minute.[7] Frequently, especially with the larger doses, a dilatation of the heart was observed. Elevation of the T-wave and of the R-T interval as described previously on the intact animal was a constant feature in these experiments.

GENERAL CARDIAC ANOXEMIA AND EXCESS OF CO_2

Anoxemia was produced either by administration of potassium cyanide in doses which would arrest the oxidative processes or by replacing the normal blood in the apparatus by thoroughly deoxygenated blood. In

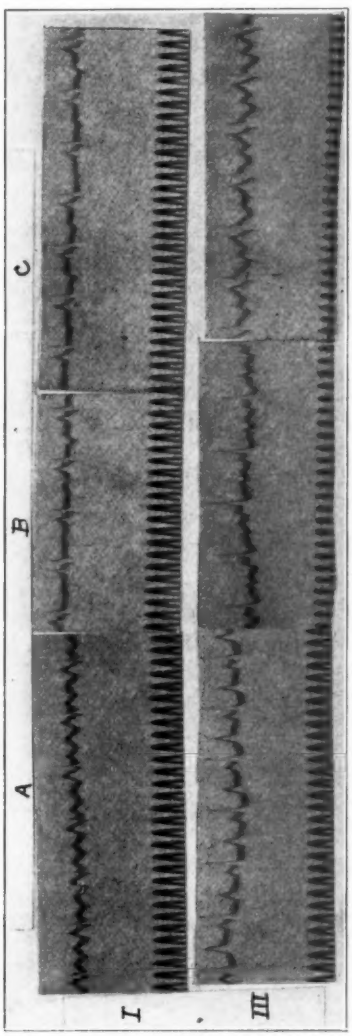

Fig. 1.—The effect of anoxemia on the electrocardiogram. There is a progressive diminution in size and inversion of the T-waves. No change in the R-T interval was noted. *A*, Leads I and III taken at the beginning of the experiment; *B*, Leads I and III taken two and three minutes after *A*; and *C*, Leads I and III taken five and six minutes after *A* when the heart had dilated.

neither case were the changes in the electrocardiogram like those observed in asphyxia. The T-wave became small in all leads and remained small until heart-block or ventricular fibrillation ensued. No change in the R-T interval was noted in our experiments, although in some of them anoxemia was allowed to continue until the heart dilated and the blood pressure fell much the same as it did in the case of asphyxia. When fresh blood was substituted for the deoxygenated or for the cyanide

blood before the appearance of complete heart-block or of ventricular fibrillation, the physical appearance of the heart and the electrocardiogram returned to normal.

The effect of CO_2 on the heart was studied by substituting oxygenated blood containing 80 vol. per cent of carbon dioxide (P_H 7) soon after respiration had been shut off. The blood when passed through the heart was collected and was not permitted to flow back into the venous reservoir. Any effect on the electrocardiogram of the reduced oxygen to the heart was thus avoided. There was a marked dilatation of the coronary vessels, and many extrasystoles arose in both ventricles and auricles. The heart dilated when exposed to the increased CO_2 tension and the output diminished. The electrocardiogram showed runs of extrasystoles. The extrasystoles were often so numerous that the curves looked as though the ventricles were fibrillating. However, when arterial blood was substituted for blood containing CO_2 the curves returned to normal. Some of the records showed an increase in ventricular conduction time early in the experiments. The T-waves were high or deeply inverted. No change in the R-T interval was observed.

LOCAL CARDIAC ASPHYXIA ANOXEMIA AND EXCESS OF CO_2

For these experiments the three main branches of the coronary system were carefully dissected as close to their origin as possible. The right coronary artery, the circumflex branch, and the descending branch of the left coronary artery were surrounded by ligatures by pulling on which it was possible to obstruct any of the three branches. Clamping of any of the coronary arteries produced in our experiments varying pictures in the electrocardiogram in different animals. This is most probably determined by the different development of the collateral circulation between the arteries. It has been shown by previous observers that anastomoses in the coronary system, although well developed in the dog's heart, show considerable variations from one animal to another.[1]

Repeated clamping of the right coronary artery was performed in twelve animals. In six it showed an increase in size of the T-wave in all leads. In five it produced an increase in the T-wave in Lead I with a decrease or an inversion of the wave in Lead III. In one case the T-wave was found to be inverted in Lead I and high in Lead III. In all cases, however, the R-T segment showed a slight depression in Lead I and an elevation in Lead III.[1]

Clamping of the circumflex branch of the left coronary artery showed likewise many different effects in regard to the T-wave. The most common one observed was a tendency to a lowering or an inversion of the T-wave in Lead I which was progressive as the period of clamping increased.[7] In some instances the T-wave remained unchanged and a change in the R-T segment alone was noted. The R-T interval was elevated in Lead I; this change was usually so marked that the T-wave

branched from the QRS complex. The S-T segment was depressed in Lead III.

Clamping of the descending branch of the left coronary artery produced the most variable changes of all vessels clamped.[8] Shortening of P-R interval or inversion of the P-wave was of common occurrence. Frequently the heart rate slowed during the period of clamping. Inversion of the T-wave in all leads was usually the common finding, although inversion in Lead I with an elevation in Lead III occurred in a certain number of cases. A conspicuous change in the R-T interval with an elevation in all leads was most common, although an elevation of the S-T segment in Lead III and an inversion of it in Lead I sometimes occurred. An increased duration of the QRS complex was noted in the majority of our experiments indicating an involvement of the conducting system of the ventricles.

Similarly to the case of general asphyxia of the heart muscle, clamping of the coronary artery also produces a conglomerate of changes which cannot be interpreted without further analysis. Too many factors operate simultaneously, and it is again difficult to decide which of them are mainly responsible for the changes in the electrocardiogram. The immediate effect of clamping an artery is an acute drop of blood pressure in the periphery including the capillaries. We consider that this factor is of no significance in regard to the changes observed in the electrocardiogram and this for the following reasons: A sudden drop of blood pressure in the perfused coronary arteries of a heart lung preparation does not bring about any change in the electrocardiogram so long as this drop of blood pressure is not sufficiently prolonged to bring about an asphyxial state. The maximum drop of blood pressure peripherally to the place of clamping is observed within a very short time after the beginning of occlusion. The changes in the electrocardiogram, however, develop gradually and are progressive. The cause of these changes must be looked for among those chemical processes which result on deprivation of the blood supply and lead to fundamental disturbances of the cardiac activity. Similarly to the general asphyxia in the case of clamping an artery, we deal again with anoxemia, with accumulation in the tissues of various known products of metabolism such as carbonic and lactic acids and of other products hitherto unknown but strongly suggested by various observers.[11] The following attempts were made to differentiate between the possible factors in order to find the one which is responsible for the change in the R-T segment. The coronary arteries in the heart lung preparation were carefully dissected and prepared for insertion of cannulae.[12] The cannulae were connected with a reservoir containing blood. By raising or lowering the reservoir the blood pressure in the perfused coronary artery could be changed within wide limits. By changing the blood in the reservoir it was possible to perfuse the coronary artery with blood of any desired composition. In all these

experiments the external work of the heart was constant, that is, its output and the arterial resistance remained the same. The blood perfusing the coronary arteries was warmed on the way from the reservoir to the same temperature as the blood entering the cavities of the heart.

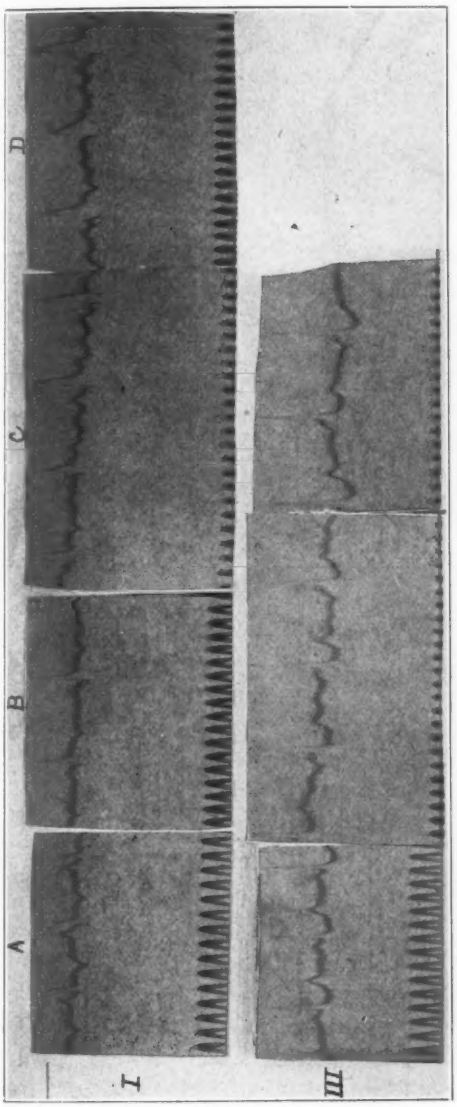

Fig. 2.—The effect of ligation of the descending branch of the left coronary artery in the heart-lung preparation. *A*, Leads I and III taken at the time of ligation; *B*, taken forty seconds after ligation; *C*, seventy seconds after ligation, and *D*, ninety seconds after ligation. A slight elevation of the S-T segment in Lead I and depression of the segment in Lead III. Inversion of the P-wave within forty seconds was noted. Increase in the QRS duration began at eighty seconds and continued until one hundred twenty seconds when the heart passed into complete heart-block. The T-wave inverted in Lead III.

The switching over of the coronary blood supply from normal to the perfusion reservoir did not bring about any change in the electrocardiogram whatever. In several experiments the right and left coronary arteries were supplied from two different reservoirs so that asphyxial blood

could be introduced in one of the arteries while the other continued to be perfused with normal blood.

Perfusion of the left coronary artery with asphyxial blood produced an inversion of the T-wave in Lead III and a high upright T-wave in Lead I. The R-T interval was elevated in Lead I and depressed in Lead III.

Perfusion of the right coronary artery with asphyxial blood produced an inversion of the T-wave in Lead I and an elevation of it in Leads II and III. The R-T interval was depressed in Lead I and elevated in Lead III. The side of the heart which was perfused with asphyxial blood showed unmistakable signs of dilatation, and, if the perfusion was prolonged, ventricular fibrillation took place.

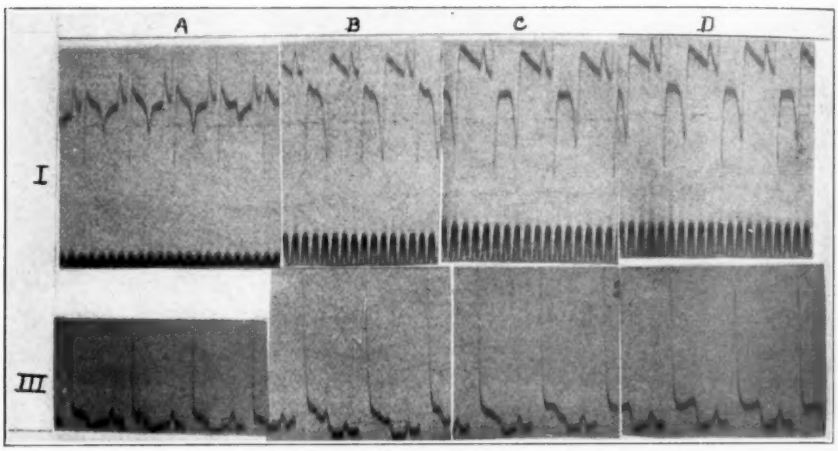

Fig. 3.—The effect on the electrocardiogram of perfusion of the right coronary artery with asphyxial blood. *A*, two minutes after perfusion began; *B*, three minutes; *C*, four minutes; *D*, five minutes. When the left coronary artery was perfused, the opposite change occurred, elevation of the R-T segment in Lead I and depression of S-T segment in Lead III.

In order to determine whether anoxemia was the sole operative factor in producing these changes, the coronary blood vessels were perfused with blood containing potassium cyanide in concentration of 1.0 millimol. Perfusion of either of the coronary blood vessels with cyanide blood did not produce changes in the electrocardiogram which were comparable with those resulting from perfusing with asphyxial blood. A decrease in size and an inversion of the T-waves in all leads was noted. In some experiments the perfusion with cyanide blood was carried until the point of prefibrillation was reached, but no definite changes in the R-T interval could be detected.

Oxygenated blood containing 80 vol. per cent of carbon dioxide (P_H 7) was perfused through the coronary blood vessels. No change in the R-T interval took place, and the T-wave became conspicuous. There was noted a development of ventricular extrasystoles arising on the per-

fused side; they usually developed soon after the perfusion with CO_2 rich blood was started and continued until fresh blood was readministered.

The results of the experiments described in this communication show that anoxemia and excess of CO_2 acting on the heart separately fail to reproduce the electrocardiographic change seen in coronary asphyxia. At the present state of our knowledge it is impossible to advance any

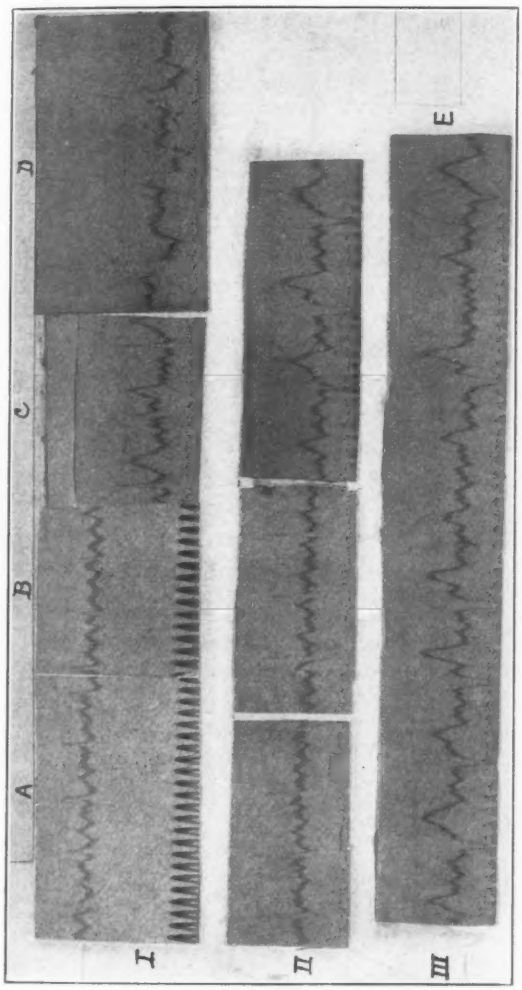

Fig. 4.—Arterial blood saturated with 80 vol. per cent carbon dioxide substituted for normal blood perfused through the left coronary artery. *A*, Leads I and III before perfusion; *B*, Leads I and III thirty and forty seconds later; *C*, Leads I and III ninety and one hundred ten seconds after perfusion began; *D*, one hundred thirty to one hundred forty-five seconds; and *E*, Lead III one hundred sixty seconds after perfusion began. A marked increase in size of T-wave in Lead III with but little change in the R-T segment. Many runs of ventricular extrasystoles were noted.

definite suggestion in regard to the real cause of the changes in the R-T interval observed during asphyxia. It is possible that the additive action of anoxemia with excess of CO_2 may account for the electrocardiographic change.[9] It is, however, also possible that the change is due to some third factor such as an accumulation of metabolites in the tissue. Although perfusion of the heart with anoxemic blood would lead to the

production of these metabolites, it would prevent their accumulation on account of being washed off with the blood supplying the capillaries. Increase of CO_2 in the blood would lead to an increased CO_2 tension in the tissues, but on account of the oxygen still being present a large accumulation especially of abnormal products of oxidation would not take place.[10] In coronary occlusion, however, these metabolites would be produced and not washed out of the tissue. Just as in the case of administration of blood removed from an asphyxiated animal of another heart lung preparation, the metabolites in addition to those produced by the heart would be administered to the heart muscle from external sources.

SUMMARY

Perfusion of coronary arteries of the dog with asphyxial blood produces changes in the electrocardiogram similar to but more marked than those produced by clamping the coronary arteries. These changes in the electrocardiogram are found to be comparable to those observed in coronary diseases in the human heart. Neither anoxemia nor excess of CO_2 separately produces the changes observed in asphyxia. Administration of cyanide, producing the severest form of anoxemia, also fails to produce these changes.

It is suggested that the change in the R-T segment typical of experimental asphyxia of the heart and probably of human coronary disease is due to a high concentration of locally produced metabolites. Perfusion with anoxemic blood tends to lower or invert the T-waves of the electrocardiogram in different leads depending upon which ventricle is affected. Excess of CO_2 increases the size of the T-wave in all leads and causes a development of ventricular foci.[10]

The authors are indebted to Professor G. V. Anrep for his help and criticism during the performance of these experiments.

REFERENCES

1. Barnes, A. R., and Mann, F. C.: Proc. Staff Meetings Mayo Clinic **6**: 269, 1931.
2. Kountz, W. B., and Gruber, C. M.: Proc. Soc. Exper. Biol. & Med. **27**: 170, 1929.
3. Smith, F. M.: Arch. Int. Med. **22**: 8, 1918.
4. Katz, L. N., Feil, H. S., and Scott, R. W.: Am. Heart J. **5**: 11, 1929.
5. Smith, F. M.: Arch. Int. Med. **25**: 673, 1920.
6. Green, Chas. W., and Gilbert, N. C.: Am. J. Phys. **60**: 155, 1922.
7. Gruber, C. M., and Kountz, W. B.: J. Pharmacol. & Exper. Therap. **40**: 253, 1930.
8. Feil, H. S., Katz, L. N., Moore, R. A., and Scott, R. W.: Am. Heart J. **6**: 522, 1931.
9. Andrus, E. C.: J. Physiol. **59**: 361, 1924.
10. Carter, E. P., Andrus, E. C., and Dieuaide, F. R.: Arch. Int. Med. **34**: 669, 1924.
11. Lewis, Thomas: Lancet **1**: 1138, 1931.
12. Anrep, G. V., Blalock, A., and Hammouda, M.: J. Phys. **67**: 87, 1929.

PAROXYSMAL HYPERTENSION ASSOCIATED WITH A GANGLIONEUROMA OF THE SUPRARENAL MEDULLA*

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TUMORS of the suprarenal medulla have been noted in several cases in conjunction with paroxysmal hypertension, vasomotor and gastric disturbances, and other phenomena apparently dependent upon an autonomic imbalance. This association has suggested a definite clinical syndrome, with the tumor as the etiological factor. Suprarenal medullary tumors have been classified by Oppenheimer and Fishberg[1] as: sympathoblastomas, composed of immature sympathoblasts; ganglioneuromas, composed of relatively mature sympathetic ganglion cells; and paragangliomas, composed of apparently mature chromaffin cells. It has usually been in association with these latter tumors that paroxysmal hypertension has been recorded. Cases have been described as follows:

Labbé, Tinel and Doumer[2]: A woman of twenty-eight years suffered from attacks initiated by malaise, pallor and coldness and extreme vasoconstriction of the extremities. Next occurred a sensation of epigastric constriction, with nausea and vomiting, followed by palpitation and increased heart rate. The attacks terminated with extreme vasodilatation and profuse sweating, leaving the patient exhausted. Between attacks the blood pressure was 15 systolic, 10 diastolic (Pachon sphygmomanometer). During attacks it rose to systolic 26-28, diastolic 16-19, in other words, to nearly double the ordinary pressure. Death occurred during an attack of pulmonary edema. Autopsy revealed a paraganglioma as the only significant finding.

Labbé, Azérad and Violle[3]: A man of twenty-nine years for ten years had attacks similar to those of the previous case, associated with similar paroxysms of hypertension. A right hemiplegia resulted from one attack, and death occurred during another. Autopsy showed a paraganglioma of the suprarenal.

Oberling and Jung[4]: A woman of twenty-eight years, near the end of a second pregnancy, had severe headache and some albuminuria. The blood pressure showed considerable fluctuations, 250 mm. systolic and 190 mm. diastolic to 170 mm. systolic and 110 mm. diastolic. The delivery was normal, but the patient died shortly after in shock. At postmortem examination a paraganglioma of the left suprarenal was found.

Rabin[5]: A man of forty-five years for many years had hypertension and nervous manifestations similar to those of exophthalmic goiter.

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The blood pressure was variable, from 226 mm. systolic and 108 mm. diastolic to 177 mm. systolic and 122 mm. diastolic. After a week of fever, he developed signs of meningitis, and died, with a clinical diagnosis of Grave's disease with chronic nephritis and hypertension. Autopsy showed normal thyroid and kidneys; generalized arteriosclerosis; cardiac hypertrophy; chronic passive congestion of the viscera; lung infarcts. There was a pheochromocytoma of the right suprarenal medulla, with areas of necrosis and hemorrhage and venous thrombi. Although definite paroxysms of hypertension with marked vasomotor disturbances were not noted, the marked variations in blood pressure with the evidences of autonomic imbalance are suggestive.

Vaquez, Donzelot and Geraudel[6, 7]; Laubry [8]: A man of thirty-seven years suffered from attacks of severe abdominal and thoracic pain; marked vasomotor disturbances and paroxysms of hypertension. He was treated with radiotherapy to the lumbar region. The attacks disappeared, to recur six months later and to disappear again, following further irradiation. They again recurred, and the patient died suddenly in a condition resembling that of uremic coma. Autopsy revealed a paraganglioma of the right suprarenal. The kidneys and other organs were normal.

Shipley[9]: A woman of twenty-six years had attacks consisting of precordial pain, palpitation, headache, nausea, vomiting, diarrhea, vasomotor phenomena and paroxysms of hypertension. She was operated upon, with removal of a paraganglioma of the right suprarenal. There was considerable shock attendant upon this operation, but the patient recover uneventfully, and ten months later was still entirely free from attacks.

Mayo[10]: A woman of thirty years had attacks of dyspnea, palpitation, thoracic and abdominal pain, headache, pallor, and numbness and coldness of the extremities. During attacks the blood pressure rose from 130 mm. systolic and 82 mm. diastolic to 300 mm. systolic and 180 mm. diastolic. At operation a tumor, which appeared to be an enormous sympathetic ganglion, was found behind the tail of the pancreas, and removed. Microscopically, it somewhat resembled a suprarenal cortical adenoma, but was not characteristic and was finally diagnosed as a retroperitoneal malignant blastoma. Following the operation there was immediate, complete and permanent relief of symptoms, and the systolic blood pressure was never found to exceed 120 mm.

Porter and Porter[11]: A man thirty-nine years old had had attacks, precipitated especially by lying on the left side, of nausea and ashen pallor, during which the blood pressure rose from a systolic of 110 to more than 200 mm. in 90 seconds. At operation an alveolar carcinoma of the adrenal cortex was found. The operation was followed by profound shock, but the patient made a complete recovery; there

was no recurrence of the attacks, and he could lie on the left side without discomfort.

In six of the above eight cases a tumor of the suprarenal medulla was demonstrated at autopsy or at operation. In this connection Rabin's conclusions, drawn from a series[5] of 30 cases of such tumors, are of considerable interest: The tumor is a neoplastic growth, benign, encapsulated, nonmetastatic, which has a cellular structure similar to that of the normal suprarenal medulla. It appears to be actively secretory; the chromaffin reaction evidences a strong reducing substance probably epinephrine. Epinephrine was always present when qualitative tests were made. Quantitatively, it was found in larger amounts than in the normal suprarenal. Other associated findings were: nine cases of hypertension independent of renal disease; arteriosclerosis found regularly in the cases associated with hypertension; glycosuria in four cases, in two of which the pancreas was proved normal at autopsy, in the other two of which its condition was not stated; many cases showing symptoms of vasomotor or sympathetic instability or severe shock incommensurate with its apparent cause; four cases of neurofibromatoses. Rabin points out that although epinephrin could cause many of these symptoms, yet increased absorption has never been proved, although the vascularity of the tumor is suggestive; proof of a casual relationship between the tumor and the clinical state requires the demonstration of a hyperadrenalinemia, which is not possible with present methods.

Vaquez, Donzelot and Geraudel[7] point out that the explanation becomes more complicated in the case of a cortical tumor, which throws discredit on the theory of hyperadrenalinemia. They feel that this argument becomes less important if one considers there is grave doubt as to the embryological and physiological duality of the suprarenal parenchyma.

In explanation of the gastric symptoms, Labbé, Tinel and Doumer suggest either mechanical irritation by the tumor or more probably a local vasoconstrictive crisis associated with the peripheral vasoconstriction.

REPORT OF CASE

Patient L. Z., male, aged forty-six years, an Italian furrier, was admitted to the First Medical Division of the New York Hospital on Nov. 6, 1930.

The family history and past history were not significant.

For nine years the patient had been subject to attacks of nausea, vomiting, numbness, dizziness and pallor, followed by flushing and profuse sweating. During the past two or three years the following other conditions had arisen: (1) Several sore throats diagnosed as tonsillitis. (2) Slight cough and occasional hemoptysis. (The sputum was repeatedly negative for tubercle bacilli.) (3) Polydipsia, polyuria, nocturia, polyphagia and occasional intense itching. (4) Loss of twenty pounds in weight. (5) Loss of sexual power. (6) Palpitations, not related to effort.

Physical Examination.—The patient was a moderately well nourished man forty-six years old, with florid complexion and grayish white hair, who appeared older

than his given age. The significant findings included: (1) Enlargement of the heart to the left (12.5 cm.). Rate 90, rhythm regular. (2) There was a soft systolic murmur at the apex, and at the right of the sternum in the second intercostal space. (3) The arteries were markedly sclerotic. Ophthalmoscopic examination showed marked arteriosclerosis and endarteritis, haziness of the discs, scars of old hemorrhages and several fresh hemorrhages. (4) The blood pressure on admission was 160 mm. systolic, 120 mm. diastolic. (5) The liver edge was palpable below the right costal margin. (6) A mass in the left upper quadrant, thought to be spleen, was palpable on deep inspiration.

Detailed Account of Attacks.—Sometimes precipitated by turning or bending, at other times without discernible cause, the attacks would grip the patient with startling suddenness. At the onset the patient would become weak and dizzy, and complain of numbness of the extremities; his usual florid coloring would change completely to one of marked pallor, and the extremities would become cold and have a mottled appearance. Soon there would be a feeling of nausea frequently followed by vomiting. Later, with relief of the subjective sensations, the patient would become very flushed and a profuse diaphoresis would occur, such as to drench the clothing and bed. Marked fluctuations in blood pressure accompanied these symptoms, for example, immediately after the onset of one attack, the blood pressure was found to be 280 mm. systolic and 180 mm. diastolic. The patient complained of numbness, weakness and nausea. He denied pain, headache or visual disturbance. He was pale and the extremities were cold and had a mottled purplish appearance. There was a moderate tremor of the hands. The apex beat was forcible, the rate 100, regular in rhythm. Ten minutes later the blood pressure was 250 mm. systolic and 150 mm. diastolic. There was marked subjective improvement, the color became flushed and there was a diaphoresis. The pulse was 90, regular in time, but alternate beats felt strong and weak. Thirty minutes after the onset the blood pressure was 130 mm. systolic and 98 mm. diastolic. The pulse rate was 100. Fifteen minutes later a similar attack occurred, the blood pressure reaching 270 mm. systolic and 180 mm. diastolic. It fell in twenty minutes to 118 mm. systolic and 90 mm. diastolic.

At times the attacks assumed a milder form, consisting of either vasomotor or gastric disturbances alone, or of any combination of the two. They occurred frequently, sometimes several times a day. As stated above, the only causative factor which the patient had noticed in this connection was change in position, and for years he had been afraid to lie on his left side lest this should precipitate an attack.

Laboratory Findings.—Blood count: red cells 4,750,000, hemoglobin 65 per cent, white cells 11,600, polynuclears 75 per cent, lymphocytes 25 per cent. Urine: cloud of albumin, sugar four plus, no acetone. Blood sugar 375 mg. per 100 c.c. Blood urea nitrogen 13 mg. per 100 c.c. Blood Wassermann reaction negative. Sputum negative on three occasions for tubercle bacilli. X-ray films of lungs showed no evidence of pulmonary disease but did show what was apparently a muscular weakness of the left diaphragm, confirmed by fluoroscopy, and suggestive of an early eventration. Fluoroscopy of stomach showed a narrowed appearance of the antrum. There was a large indefinite mass on the left, thought possibly to be spleen. Basal metabolic rate 23 per cent above average normal. Red test for kidney function: 35 per cent excretion of the dye two hours after intramuscular injection. Pulse rate 70-100. Successive electrocardiograms on various occasions showed many variations: Normal sinus rhythm; premature auricular beats; inversion of T-wave of coronary type in the first two leads; no inversion; left axis deviation of QRS; no axis deviation of QRS.

Course.—The patient was given a diabetic diet and insulin. It was found rather difficult at times to differentiate a mild attack of the patient's usual type from mild insulin shock. Before discharge there was occasionally one or two plus sugar in the

early morning specimen. The others were negative. The blood sugar was 180 mg. on discharge. The diet was carbohydrate 140 gm., protein 80 gm., fat 70 gm. Insulin 62 units a day. During the patient's stay the attacks diminished in frequency and intensity, but were still troublesome. He was discharged Dec. 6, 1930.

Because the patient's clinical syndrome of vasomotor and gastric disturbances, associated with signs of instability of the vegetative nervous system, especially the paroxysmal hypertension, so closely resembled the syndrome associated with cases of suprarenal tumor as described in the literature, it was believed that the patient was suffering from this condition. The exact etiology of the hyperglycemia and glycosuria could not be determined. The possibilities were considered of an independent diabetes; of a sclerosis of the pancreas associated with the marked arteriosclerosis found elsewhere; of a hyperglycemia dependent upon a hyperadrenalinemia. On the basis of a diagnosis of adrenal tumor the advisability was considered of surgical removal of the tumor, as was done successfully in the cases cited above. However, it was felt that the patient's general condition was not good enough to warrant operative interference. Such cases are at best subject to severe shock from even minor operative procedures, and the present case was complicated by the diabetic condition and the marked arteriosclerosis. As Laubry obtained considerable relief in a similar case by irradiation of the adrenal region, it was decided to use x-ray treatment in the present case, after which, if improvement occurred, surgery might be reconsidered.

Under the supervision of Dr. John R. Carty x-ray treatment was given as follows: "Medium wave aluminum filtered radiation at 130 K.V.P. applied posteriorly over the suprarenal region on each side. Each area received four treatments from Feb. 11, 1931, to April 22, 1931, averaging approximately three-quarters of a skin erythema dose at each treatment. Slight improvement was noted following the last treatment; subsequently the patient went downhill."

The attacks continued during the treatment. Following the development of an infection of the hand and a corneal ulcer, hospitalization was advised, but declined, as the patient felt he must try to continue work. He could not follow dietary directions, so continued to have glycosuria, polydipsia and polyuria. July 12, 1931, he re-entered the hospital in a moribund condition. There was congestive heart failure with dyspnea, orthopnea, vomiting, pulmonary congestion, pleural effusion and edema. He died within two hours of admission.

Autopsy Findings.—Heart: hypertrophied, weighing 600 gm. Aorta: marked atheroma. Lungs: congested. Bilateral pleural effusion. Stomach: dilated with four liters of dirty yellow fluid. Liver: congested. Spleen: thickening of arterial and arteriolar walls. Pancreas: normal except slight increase in fibrous tissue and thickening of the walls of the smaller arteries. The islands of Langerhans were well marked and normal in appearance. Kidneys: the cortex was somewhat reduced on section, and microscopically there were changes compatible with mild chronic vascular nephritis. Right adrenal: normal.

A tumor, the size of a large grapefruit, was found retroperitoneally in the left upper quadrant, displacing the kidney downward and the left dome of the diaphragm upward. The tumor derived its blood supply from the abdominal aorta, above the left renal artery. It was attached by a pedicle to the midline structures. In removing it a portion of what was apparently the left adrenal was found in the adjacent tissues, but its exact relation to the tumor could not be demonstrated. The smooth surface of the tumor was covered with dilated veins, and there was a thick fibrous capsule. There were a few cysts just inside the capsule and the center of the mass was necrotic. Microscopically, the tumor was composed of masses of cells having a rather striking resemblance to those of the suprarenal medulla. The cells were large, irregular, with bluish staining cytoplasm which strung out into fibrils. The large ovoid nuclei had prominent nucleoli. The cells were arranged loosely in

lobes and lobules with dense fibrous capsules. Their resemblance to nerve tissue ganglionic cells would seem to point to ganglioneuroma, originating in the adrenal medulla, as the most probable diagnosis. A stain for chromaffinity was negative.

The left adrenal was found among the tissues adjacent to the tumor as previously described. Microscopically, it showed normal cortical and medullary cells, but near its torn edge appeared a heaping up of the medullary cells to form an abnormal looking nodule surrounded by thinned-out cortex. In the light of the resemblance of these cells to those of the tumor this hyperplasia would seem significant.

SUMMARY

1. A review has been given of several cases of suprarenal medullary tumors, one cortical tumor and one retroperitoneal malignant blastoma, somewhat resembling a suprarenal tumor, which were associated with paroxysmal hypertension, gastric disturbances, and various symptoms of imbalance of the vegetative nervous system.

2. A report has been given of a case of ganglioneuroma of the suprarenal medulla associated with evidences of imbalance of the vegetative nervous system: (a) vasomotor phenomena, notably paroxysms of hypertension, followed by profuse sweating; (b) disturbance of the carbohydrate metabolism in the absence of a pancreatic lesion; (c) elevation of the basal metabolic rate; (d) gastric disturbances.

3. Treatment: Medical treatment has universally been reported as ineffectual. X-ray therapy was palliative but not curative in the case of Vaquez[6, 7] and Laubry.[8] In the present case it was only slightly palliative. Surgical removal of the tumor has produced a cure in three cases and seems the most promising mode of treatment.

REFERENCES

1. Oppenheimer and Fishberg: Association of Hypertension With Suprarenal Tumors, Arch. Int. Med. **34**: 631, 1924.
2. Labbé, Tinel and Doumer: Crises solaires et hypertension paroxystique en rapport avec une tumeur surrènale, Bull. et mem. Soc. mèd. d. Hôp. de Paris **46**: 982, 1922.
3. Labbé, Azérad and Violle: Adénome médullaire surrènale et hypertension paroxystique, Bull. et mem. Soc. méd. d. Hôp. de Paris **53**: 952, 1929.
4. Oberling and Jung: Paraganglioma de la surrènale avec hypertension artèrielle, Bull. et mém. Soc. méd. d. Hôp. de Paris **51**: 366, 1927.
5. Rabin: Chromaffin Cell Tumor of Suprarenal Medulla (Pheochromocytoma), Arch. Path. **7**: 228, 1929.
6. Vaquez and Donzelot: Crises d'hypertension artèrielle paroxystique, Presse mèd. **34**: 1329, 1926.
7. Vaquez, Donzelot and Geraudel: Le surrénalome hypertensif, Presse méd. **37**: 169, 1929.
8. Laubry: Hypertension paroxystique guérie par la radiothérapie de la région surrènale, Bull. et mem. Soc. méd. d Hôp. de Paris **51**: 1216, 1927.
9. Shipley: Paroxysmal Hypertension Associated With Tumor of Suprarenal, Ann. Surg. **90**: 742, 1929.
10. Mayo: Paroxysmal Hypertension With Tumor of Retroperitoneal Nerve, J. A. M. A. **89**: 1047, 1927.
11. Porter and Porter: Paroxysmal Hypertension Cured by Removal of Adrenal Tumor, Surg, Gynec. & Obst. **50**: 160, 1930.

AN AMPLIFIER FOR HEART SOUNDS OPERATING ON ALTERNATING CURRENT*

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VACUUM tube amplifiers for heart sounds employing either multiple headphones or a loud-speaker, have been described by many workers during the past decade. In this country interest in the amplification and registration of heart sounds was stimulated by the work of Williams[1] and Squier, reported by Winters,[2] in 1921. Within the next five years Cabot,[3] Cabot and Dodge,[4] Frederick and Dodge,[5] Gamble,[6] and Gamble and Replogle[7] contributed valuable work in this field. More recently Waud[8] has described an easily constructed amplifier which enables a number of persons to listen to greatly amplified heart sounds or murmurs. In Europe even more extensive work has been done with amplifiers of body sounds. In Germany, Bass,[9] Trendelenburg,[10] Scheminzky,[11] Pierach,[12] Landes,[13] Schwarz[14] and others have reported excellent work. Duchosal[15] and Duchosal and Mozer[16] have done outstanding work in Switzerland.

Most of the amplifiers that have been devised are bulky and hardly portable. This has been true largely because of the fact that they are energized by direct current, necessitating the use of batteries. In this paper the authors wish to describe an amplifier which operates on the ordinary alternating current supply and for which no accessory batteries are required. Furthermore, the outfit is constructed entirely of parts which may be obtained from any radio supply house. It can be built by anyone at all handy with tools for a cost of not over thirty-five dollars.

The entire amplifier and loud-speaker are housed in a sturdy box of the type designed for portable radio sets. This case measures 18 by 11 by 10 inches and is procurable at radio supply houses. Fig. 1 shows the amplifier with the front piece which protects the control knobs removed. A switch for the alternating current supply is seen near the middle of the panel. Below it is the potentiometer input control. To the left are four jacks, one for the input and three for headphones in the output circuit. The control at the extreme left regulates the volume in the headphones.

A modification of the well known Loftin-White direct coupled amplifier is used. Examination of the circuit diagram (Fig. 2) shows that in addition to the usual screen grid tube directly coupled to a power amplifier an additional screen grid tube is employed. This tube is

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resistance-coupled to the others and adds materially to the sensitivity of the outfit. The constants of the resistances and condensers needed are also shown in the figure. It should be pointed out that the resistance R 9 which must have a value of 4300 ohms is obtained by using the field of the dynamic speaker and a suitable resistance either in parallel or in series with it, so that the total resistance of the combination will have the desired value. The speaker that was employed in our unit has a field resistance of 5000 ohms. To bring the resistance down to

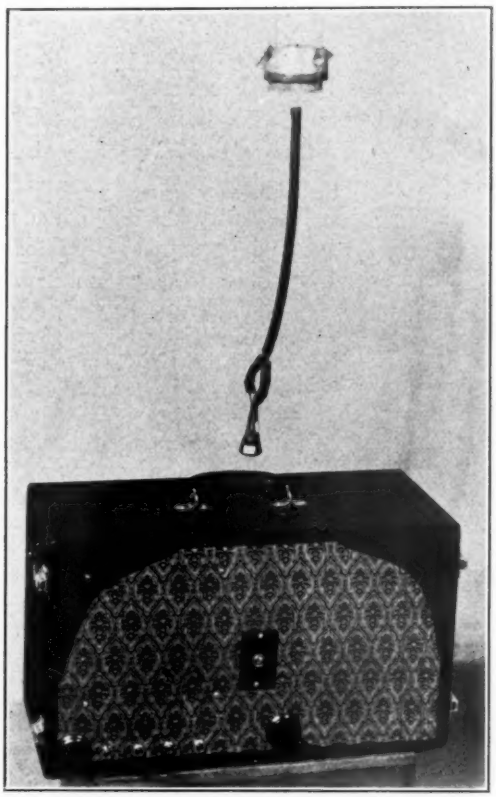

Fig. 1.

4300 ohms it was necessary to shunt the field with a resistance of about 30,000 ohms.

The chief difficulty encountered in the construction of the amplifier operating on alternating current is the elimination of the sixty cycle hum. The operation of our amplifier is quite satisfactory in this respect. The alternating current hum is scarcely audible in the loud-speaker and even with the headphones it is not objectionable until the volume is greatly increased. The large capacity of the filter condensers C 5 and C 6 and the careful grounding of the circuit at all points indicated are important factors in the elimination of alternating current hum.

An amplifier of the type described has an excellent fidelity curve. In other words, it amplifies without distortion over a wide frequency range. The results obtained with even the best of amplifiers, however, are not good unless a microphone with an equally good frequency response is employed. Microphones of the carbon, electromagnetic and condenser

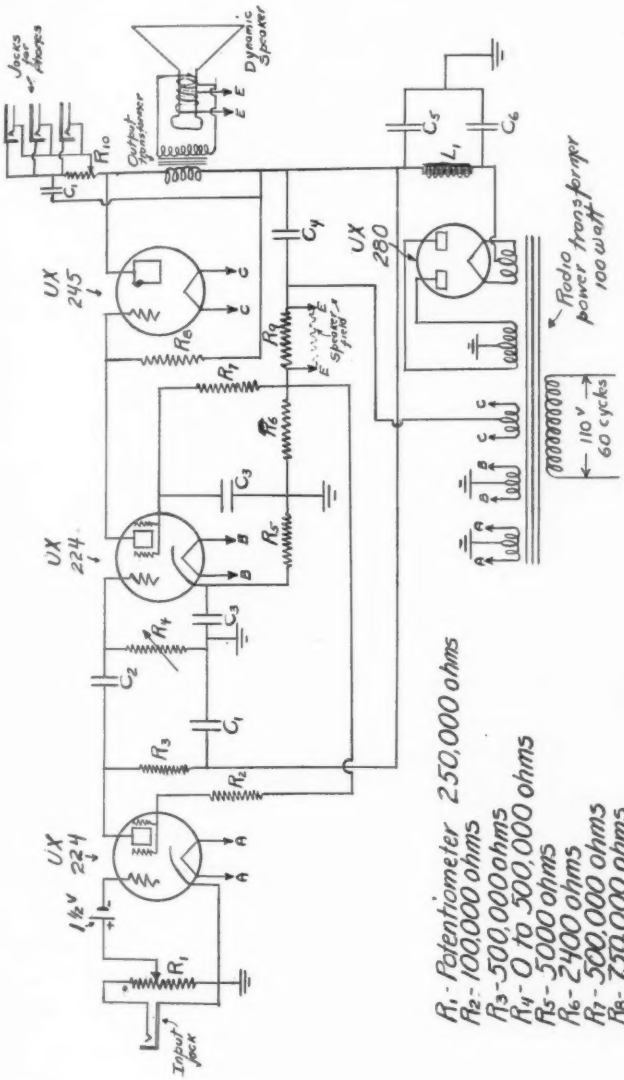

Fig. 2.

types were tried, but the latter was by far the most satisfactory. Carbon microphones, although they are very sensitive and have a fairly good frequency response, are noisy. Several types of electromagnetic units were tried but none was found which gave good quality and was at the same time sufficiently sensitive. The condenser microphone responds

equally to sounds varying from 30 up to several thousand cycles per second, and, as Cabot and Dodge[4] have shown, practically all cardiac sounds fall within this range. In addition to its excellent fidelity the condenser microphone is very sensitive. Unfortunately this microphone is not only the most expensive of the three types, but it requires the use of an additional tube amplifier which employs a direct current supply.

In using the condenser microphone it was found that if the instrument was placed directly on the chest wall many murmurs were very poorly reproduced. Apparently this was due to damping effects within the closed microphone chamber. At any rate the difficulty was obviated by connecting the microphone to a short piece of rubber tubing ending in an ordinary stethoscope bell. Fig. 1 shows the microphone and tubing arrangement suspended above the amplifier.

The rubber tubing employed was about eighteen inches long and had an inside diameter of about one-quarter inch. It was fastened to the microphone by means of a glass connector which fitted snugly into a thin cork disk of large diameter. The cork was firmly held to a sponge rubber ring (which had been glued to the microphone chamber) by means of rubber bands. At the other end of the tube different types of stethoscope bells were attached, as shown in Fig. 1. The volume of the amplified sounds was reduced materially when compared with the volume obtained with the microphone directly on the chest wall. Further investigation of the acoustic properties of the sound conducting system and various types of stethoscope attachments is in progress.

It should be mentioned that, when any amplifier having a loud-speaker is used, precautions may be necessary to eliminate "feed-back" from the speaker to the microphone. This feed-back causes howling and renders satisfactory operation impossible. With an extremely sensitive amplifier and microphone, such as we have described, complete removal of the feed-back is surprisingly difficult. The remedy quite obviously consists in preventing extraneous noise from entering the microphone. This may be accomplished by careful shielding of the microphone or by increasing the distance between amplifier and microphone until howling no longer occurs.

It should be emphasized, perhaps, that, although the amplifier (except for the single cell-1½ volt grid bias) operates entirely on alternating current, when the condenser microphone is used, batteries to supply the accessory vacuum tube are required. It is possible that further studies may enable us to use an alternating current supply for the microphone also.

When the condenser microphone is used with the amplifier, the volume of the amplified sounds is sufficient to enable them to be heard in a large room, and we believe that the instrument should be of considerable value for teaching purposes. While amplifiers that employ

multiple headphones have the advantage that the sounds come to the ear through rubber tubing and are consequently similar to sounds heard through a stethoscope, nevertheless an amplifier employing a loud-speaker is in many ways more practicable for use in teaching.

SUMMARY

A sensitive audio-frequency amplifier with a loud-speaker operating on alternating current and suitable for the amplification of heart sounds and murmurs is described. The condenser microphone has been found to be superior to other microphones for use with the amplifier.

The authors wish to acknowledge their indebtedness to Professor L. N. Holland of the Electrical Engineering Department of the University for his kindness in loaning the condenser microphone and for his helpful suggestions. We also wish to express to Dr. Frank N. Wilson our appreciation for his interest and assistance which have been invaluable in the completion of this work.

REFERENCES

1. Williams, H. B.: New Method for Graphic Study of Heart Murmurs, Proc. Soc. Exper. Biol. & Med. **18**: 179, 1921.
2. Winters, S. R.: Diagnosis by Wireless, Scientific American **124**: 465, 1921.
3. Cabot, R. C.: A Multiple Electrical Stethoscope for Teaching Purposes, J. A. M. A. **81**: 298, 1923.
4. Cabot, R. C., and Dodge, H. F.: Frequency Characteristics of Heart and Lung Sounds, J. A. M. A. **84**: 1793, 1925.
5. Frederick, H. A., and Dodge, H. F.: The Stethophone, An Electric Stethoscope, Bell System Tech. J. **3**: 531, 1924.
6. Gamble, C. J.: The Multiple Electric Stethoscope and Electric Filter as Aids to Diagnosis, J. A. M. A. **83**: 1230, 1924.
7. Gamble, C. J., and Replogle, D. E.: A Multiple Electric Stethoscope for Teaching, J. A. M. A. **82**: 388, 1924.
8. Waud, R. A.: A Heart Sound Amplifier, J. Lab. & Clin. Med. **16**: 624, 1931.
9. Bass, E.: Klin. Wchnschr. **9**: 2092, 1930.
10. Trendelenburg, Ferd: Ueber neue Erfahrungen mit der Aufzeichnung von Herztonen und Herzgerauschen, Klin. Wchnschr. **9**: 2092, 1930.
11. Scheminzky, Ferd: Ztschr. f. d. ges. exper. Med. **57**: 470, 1927.
12. Pierach, Alex.: Deutsches Arch. f. klin. Med. **171**: 235, 1931.
13. Landes, G.: München. med. Wchnschr. **77**: 591, 1930.
14. Schwarz, G.: Deutsch. med. Wchnschr. **51**: 777, 1925.
15. Duchosal, P.: Arch. d. mal. du coeur. **22**: 797, 1929.
16. Mozer, J. J., and Duchosal, P.: Arch. d. mal. du coeur. **23**: 65, 1930.

Department of Clinical Reports

CONGENITAL HEART DISEASE

Cor Biloculare*

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THE extreme rarity of pure biloculate hearts warrants the report of a single case. Abbott[1] in her statistical study of 1,000 congenital hearts analyzed only nine cases of this anomaly. The x-ray and anatomical findings of the case to be described are as instructive as they are unusual.

CASE REPORT

A. B., male, aged four months, admitted January 26, 1932, died January 26, 1932. *Chief Complaint:* Dyspnea. *Family History:* Negative. *Past History:* The child had been a "blue baby" since birth and had gained weight very slowly. He became dyspneic on the day of admission and began to foam at the mouth. The child was *in extremis* when brought to the hospital. *Physical Examination:* A marantic infant, markedly cyanotic and gasping for breath. The heart was on the right side. There were no murmurs heard. The finger nails were curved, suggestive of clubbing. The liver was enlarged. The child was placed in an oxygen tent, given stimulation, but expired an hour and a half after admission.

Roentgen Examination: An examination of the chest showed the heart to be almost entirely on the right side. It was markedly enlarged, reaching the axillary line on the right. It was globular in shape, with an irregularity on its upper right margin. (Fig. 1.) The appearance was that of a congenital heart with dextrocardia. There was only one large vessel arising from the base of the heart. This ran upward and descended to the right, disappearing in the shadow of the vertebral column.

Postmortem Examination: (Performed by Dr. E. B. Greenspan and Dr. S. Klein.) The body was that of a fairly well developed and well nourished infant of four months. There was no rigor mortis. There was marked acrocyanosis. The fontanelles were open and depressed. Both testicles were descended. *Neck:* There was a large superficial hematoma in the left side of the neck, the result of an attempt at phlebotomy. *Abdomen:* No free fluid present. The intestines, below the duodenojejunal junction, were in their normal position. The liver extended two fingerbreadths below the costal margin and was seen to extend across the entire width of the abdomen. *Chest:* Both diaphragmatic leaves reached the sixth rib. No free fluid in either pleural cavity. *Thymus:* Normal in size, position and appearance. *Lungs:* The lungs were divided into supernumerary lobes, as follows: The right lower lobe was divided by incomplete fissures into three lobes; the right middle lobe, into two lobes; the right upper lobe, into three lobes; the left lower lobe, into three lobes. There was a left middle lobe which was divided into two portions by a deep fissure. The left upper lobe consisted of only one lobe. The pleura was smooth

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and glistening. The surface of the lungs, for the most part, was pinkish red with dark blue lobular markings. Several of the small lobes, especially those located posteriorly, were firm, dark blue and did not crepitate. The remainder of the lungs was only fairly well aerated. *Gastrointestinal Tract:* The esophagus was located on the right side of the vertebral column and appeared grossly normal. The lower end of the esophagus passed through the right crux of the diaphragm. The greater curvature of the stomach was on the right, the lesser curvature reached the

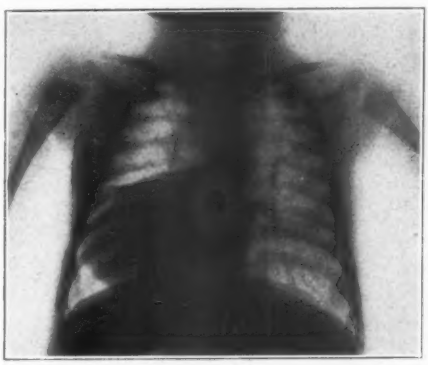

Fig. 1.—Roentgen-ray appearance of chest showing congenital heart with dextrocardia and single large arterial trunk.

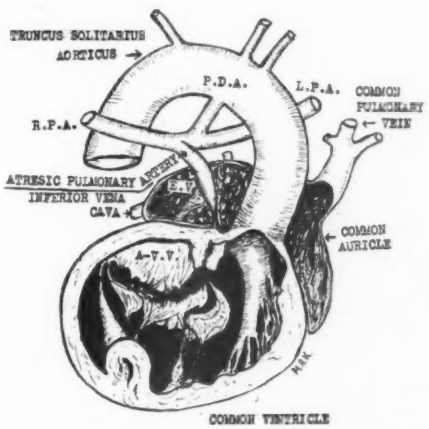

Fig. 2.—Semidiagrammatic sketch of specimen showing cor biloculare, situs inversus cordis, pulmonary artery atresia, truncus solitarius aorticus, patent ductus arteriosus (P. D. A.), common auricle, common auriculoventricular ostium with four auriculoventricular cusps (A-V. V.), eustachian valve (E. V.), right pulmonary artery (R. P. A.), left pulmonary artery (L. P. A.).

midline and a fine filmy gastrohepatic omentum extended to the right lobe of the liver from the lesser curvature. The duodenum was situated mostly in the left lower portion of the right upper quadrant and hung from a double mesentery, the base of which attached to the upper and lower borders respectively of the neck and body of the pancreas. The stomach appeared normal. The duodenum was somewhat dilated and a little longer than normal, but showed no other changes. The remainder of the gastrointestinal tract was normal grossly. In the mesentery there were many pea- to almond-sized soft, pinkish gray lymph nodes which, on section,

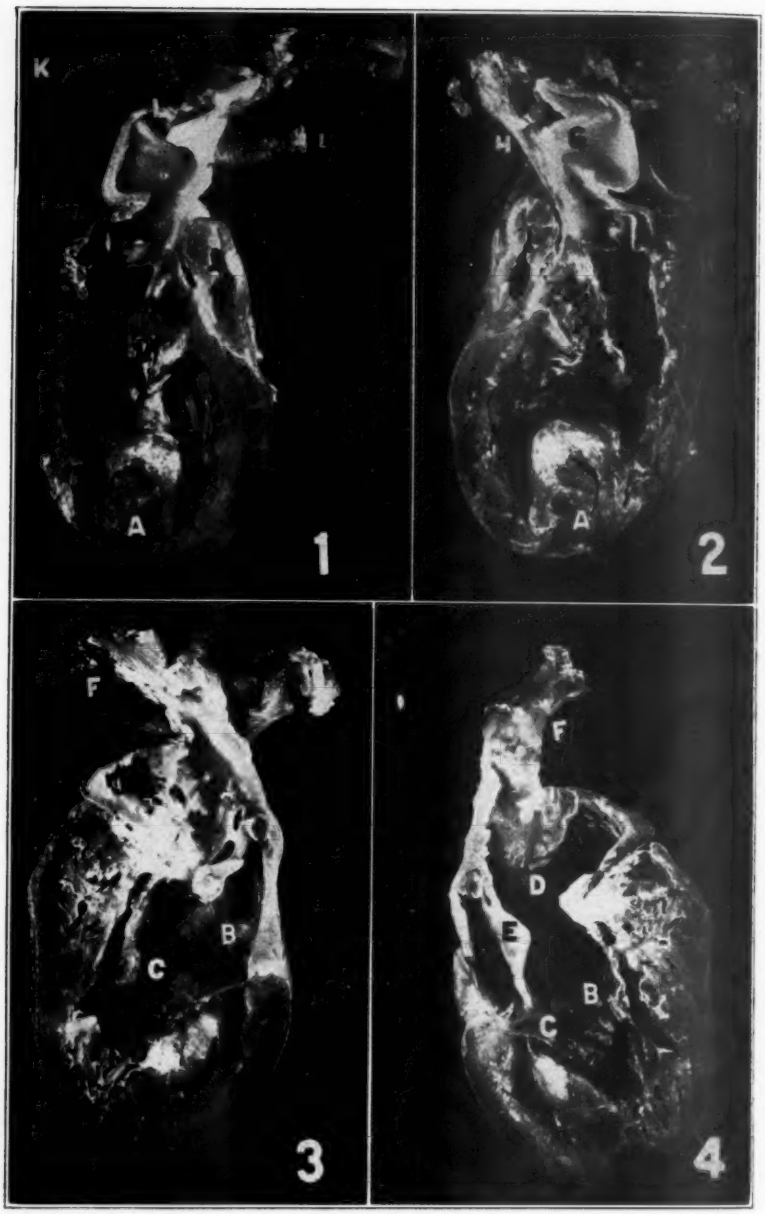

Fig. 3.—Coronal slabs cut through paraffinized heart. Anterior third (1), midportion, anterior view (2), midportion, posterior view (3), posterior third (4) of the heart showing common ventricle with rudimentary interventricular septum (A), common auriculoventricular ostium (B), with the four auriculoventricular cusps (C), common auricle (D) with hyperplastic eustachian valve (E), common pulmonary vein (F), truncus solitarius aorticus (G), atresic pulmonary artery (H), right and left branches of the pulmonary artery (K), patent ductus arteriosus (L).

presented many pinhead sized grayish nodules on a pink background. *Spleen:* The spleen and splenic vessels were not found after a careful search. In the greater omentum, extending from cardia to pylorus, and located just below and receiving branches from the gastroepiploic arch, there was a lobulated soft, pink mass, about 1 cm. in width. *Liver:* The liver was enlarged to about one and a half times its normal size. It was in the normal position. The surface was smooth. Glisson's capsule was not thickened and its color was a uniform dark purplish red. The liver had a rubbery consistency and on cut section was pale brown, somewhat wet and presented a homogeneous surface. The gall bladder and duct system were normal. The gall bladder was attached to the right lobe of the liver. *Pancreas:* The pancreas was normal in size and consistency, but its position was abnormal. The head lay on the anterior surface of the second portion of the duodenum, the neck lay behind this portion of the duodenum, and the body and tail extended to the right. *Kidney:* The kidneys were slightly enlarged and the capsule stripped easily.

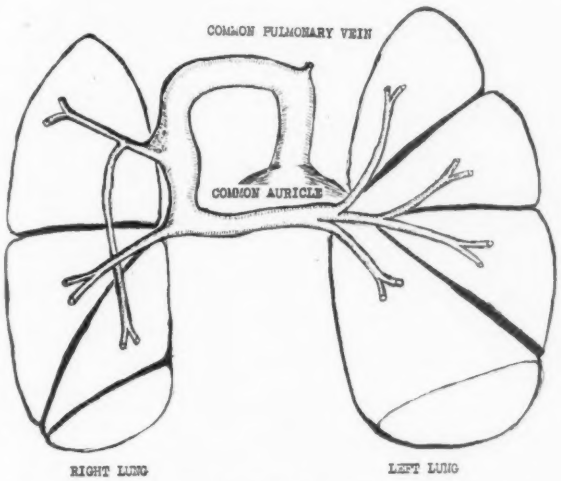

Fig. 4.—Anomalous venous circulation in the lungs.

Except for a marked congestion, they appeared normal. The ureters, bladder and prostate appeared normal. *Adrenal:* The adrenals were normal in size, shape and position. They were markedly congested.

Heart: The pericardial sac and contents were located entirely in the right chest. The long axis extended from left to right. There was no excess of pericardial fluid, and the pericardial lining was smooth and glistening.

The heart was enlarged and its apex was situated in the right part of the chest. A truncus solitarius aorticus arose from the bulbus cordis and coursed upwards and to the right over the right main bronchus, giving rise in its usual order to the innominate, carotid and subclavian arteries (Fig. 2). This vessel possessed three valve leaflets and two coronary artery orifices. The ductus arteriosus was patent and divided a short distance from its aortic origin into two branches, one going to the right and the other to the left lung. The pulmonary artery was atresic at its base. Its distal extremity became continuous with the branch of the ductus arteriosus which coursed to the right lung.

In order to preserve the topographic relations of the heart cavities, the organ was paraffinized according to the method of Gross and Leslie[3] and sectioned into three coronal slabs, i. e., anterior, midportion and posterior (Fig. 3). An examina-

tion of these slabs showed the heart to be two chambered. A common pulmonary vein entered into the left upper part of a common auricle. At the right and posterior part of this common auricle the superior and inferior vena cava entered and were separated from each other on the inner aspect of the auricle by a hyperplastic eustachian valve.

A common auriculoventricular ostium led into a single ventricular chamber. The walls of the auriculoventricular ostium bore four auriculoventricular cusps. The base of the ventricle had a small round elevation which represents the primitive interventricular septum. A muscular ridge arising from the base of the common ventricle and to the right of the primitive interventricular septum extended up the right lateral wall of the common ventricle to be inserted at the base of the aorta (Fig. 2).

The inferior vena cava was situated on the left side of the vertebral column. The aorta was smooth and elastic and was located in front and to the right of the inferior vena cava. The tributaries of the aorta were normal in position, except that the orifice of the celiac vessels was relatively narrow.

The venous circulation of the lungs also presented unusual anomalies (Fig. 4). The larger venous channels from all the lobes of the left lung united into one broad venous channel which crossed to the right and became continuous with a large venous sinus draining the right lung. This large venous channel continued cephalad and to the left to empty into the common auricle.

Anatomical Diagnosis:

1. Congenital heart disease.
   - Cor biloculare (situs inversus cordis);
   - Pulmonary artery atresia;
   - Truncus solitarius aorticus (patent ductus arteriosus);
   - Common auricle with absence of interauricular septum;
   - Hyperplastic eustachian valve;
   - Common pulmonary vein;
   - Common auriculoventricular ostium with four auriculoventricular cusps;
2. Situs inversus of esophagus and stomach.
3. Supernumerary fissures and lobes of both lungs.
4. Anomalous rotation of pancreas and duodenum.
5. Congenital absence of spleen.
6. Pulmonary congestion, edema and atelectasis.
7. Congestion of viscera.

SUMMARY

The interesting features of this case, aside from its great rarity, are the presence of the four auriculoventricular valves which represent the primitive endocardial cushions, the hyperplastic eustachian valve, the common pulmonary vein and the unusual venous circulation of the lungs. An examination of the roentgenogram of the chest revealed only a single large artery going upward and descending to the right.

The author is indebted to Dr. Louis Gross and to Dr. Maude E. Abbott for their review of this case and to Dr. Bela Schick for the use of the clinical data.

REFERENCES

1. Abbott, M. E.: Congenital Heart Disease, Nelson's Looseleaf Medicine **4**: 207, 1932.
2. Gross, L., and Leslie, E.: Paraffin Infiltration of Hearts, AM. HEART J. **6**: 665, 1931.

VENTRICULAR TACHYCARDIA WITH ALTERNATING COMPLEXES*

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IN THE last ten years nineteen instances of bidirectional ventricular tachycardia have been described. Strauss[1] in 1930 listed the reported cases, and since that time Clarke[2] has added another. Most of the cases were attributed to the action of digitalis. Some of them could scarcely

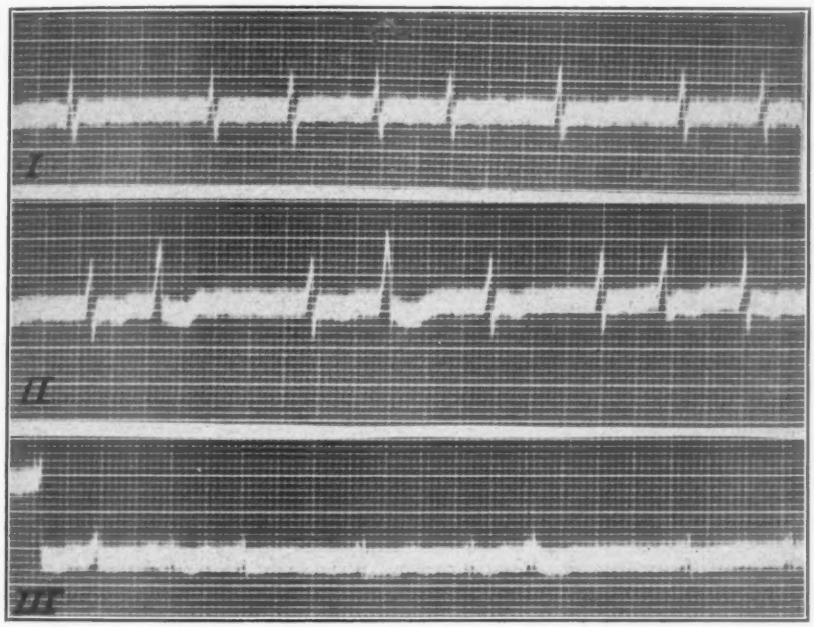

Fig. 1.—Tracing taken the day of admission, April 4, 1932, showing auricular fibrillation and occasional extrasystoles.

have been explained on this basis. There are probably other recorded cases buried in the literature under other titles. A case of this type, recently encountered in the Long Island College Hospital, presents some features which seem worthy of note.

CASE REPORT

M. L. (Hospital No. 2258) American born, a widower, a laborer by occupation, was admitted to the Long Island College Hospital, April 4, 1932, complaining of shortness of breath and swelling of the legs.

At the age of thirty years he had an attack of polyarthritis lasting for two months. At thirty-six and thirty-eight years he had recurrences of the rheumatic fever lasting several months each time.

*From the Medical Service of the Long Island College Hospital.

After the third attack he began to notice dyspnea on effort, a tendency to cough, and a variable bluish tinge to the skin.

Two years before admission he coughed up about a cupful of blood, and was taken to a hospital, where he remained nine weeks. He tried to return to work once but was unable to continue because of increasing dyspnea and palpitation. Six months before admission he had another hemoptysis. Swelling of the ankles came on about one month before admission. He was admitted to another hospital at this time, and stayed about two weeks. For two years he had been taking digitalis tablets continuously, from one to four a day.

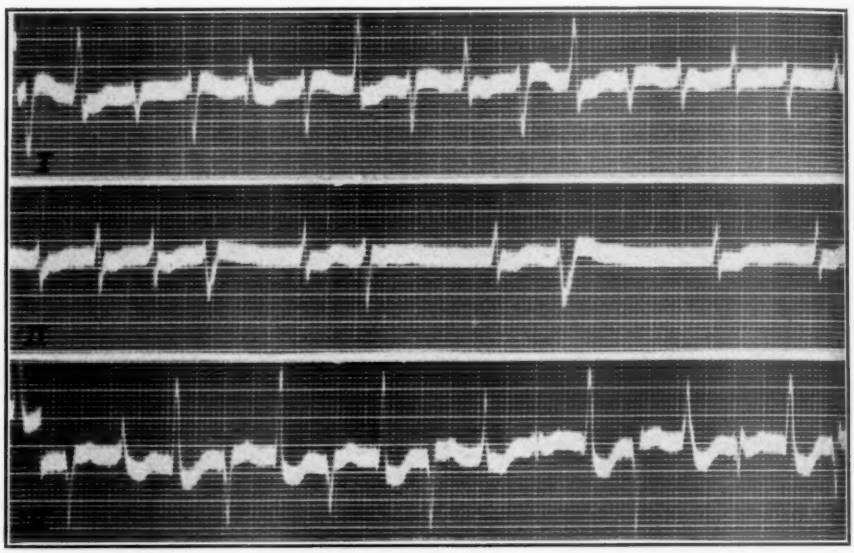

Fig. 2.—Bidirectional ventricular tachycardia. April 8, 1932. End of a paroxysm seen in Lead II. Twice in Lead I and once in Lead III the alternation reverses itself, as could scarcely happen were the mechanism one of bifocal pacemakers.

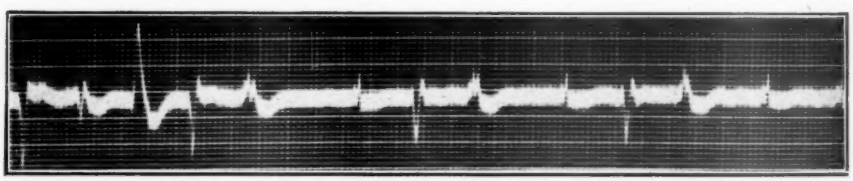

Fig. 3.—Lead III. April 9, 1932. End of a long paroxysm, followed by two paroxysms of three beats. Note the "normal" type of complex that occurs after each long pause, suggesting elapse of sufficient time for recovery of conductivity. (Cf. Robinson, G. C.: Arch. Int. Med. 18: 380, 1916.)

On examination: The temperature was 98.2°, pulse 120, respiration 42, blood pressure 100 mm. systolic, 75 mm. diastolic. He was orthopneic and cyanotic. The heart was enlarged, the borders being 5 cm. to the right and 12 cm. to the left of the midline. At the apex there was a rough systolic murmur and no second sound or diastolic murmur. No murmurs were heard at the base. The pulmonic second sound was accentuated. The rhythm was that of auricular fibrillation.

The lungs showed scattered musical râles and moist râles at the bases. The liver was enlarged and there was a dependent edema.

The day after admission the patient suffered a sudden pain in the right side

of the chest, followed by some hemoptysis and signs of an infarct. These gradually cleared up.

Course and Treatment: Digitalis was evidently indicated by the rapid heart rate in the presence of auricular fibrillation and congestive heart failure. It was known that he had been getting digitalis, but there was no way of telling how nearly digitalized he was. The electrocardiogram taken the day after admission (Fig. 1) showed only fibrillation with no clearly defined T-waves. It was decided to give him a one-grain tablet every four hours until the desired effect was obtained or toxic signs developed.

After four days he had received 1.66 gm. and his general condition had not changed very much. The heart rate was recorded as between 84 and 118. That morning the heart action was found to be alternating between a slow irregular arhythmia and rapid regular periods lasting about thirty to sixty seconds. The electrocardiogram showed these phases to be auricular fibrillation interrupted by runs of bidirectional ventricular tachycardia (Fig. 2). After this was established graphically, it was noted that on listening at the apex during the runs of tachycardia, there was a distinct alternation in the loudness of the very regular systolic sounds.

The tachycardia was ascribed to overdigitalization, and the drug was immediately stopped. The runs of tachycardia recurred frequently for several days, and as they became less frequent there were short periods of bigeminus and trigeminus, with a gradually rising pulse rate, until after a period of seven days it was necessary to resume the drug in doses of one to two grains a day. He was subsequently discharged from the hospital, able to be up and about.

COMMENT

It is suggested that the mechanism of bidirectional tachycardia depends upon a relatively fixed delay in conduction time of one branch of the bundle, while the conductivity of the other branch waxes and wanes so that it alternately slightly exceeds and fails to equal that of the first branch.

REFERENCES

1. Strauss, M. B.: Am. J. M. Sc. **170**: 337, 1930.
2. Clarke, R. M.: Calif. & Western Med. **32**: 252, 1930.

Department of Reviews and Abstracts

Selected Abstracts

Saphir, O.: Bands and Ridges in the Pulmonary Artery. Arch. Path. **14**: 10, 1932.

The study here presented is based on the examination of bands in the pulmonary artery in one case and of ridges in the pulmonary artery in another case. Both structures were encountered in the course of postmortem examinations. The first case was a patient with arterial hypertension and nephrosclerosis of the arteriolar variety who died from cardiac decompensation. There were found many bandlike structures in the pulmonary artery in addition to arteriosclerotic plaques. Histologically the bands consisted of young and old connective tissue with hyalinization. There were endothelial cells and lymphocytes present, also many red blood cells and pigmented areas. Newly formed blood vessels and blood sinuses were found throughout. The bands themselves were lined by intimal lining cells and represented organized and still organizing thrombi. In the second patient who died from cardiac decompensation associated with diffuse arteriosclerosis, nephrosclerosis of the arteriolar variety and emphysema of the lungs, ridges were found in the pulmonary artery. Histological examination showed that these ridges were organized mural thrombi covered by intimal lining cells.

These structures are supposed to be the result of organized mural thrombi. It is believed that the systolic pressure in the pulmonary artery transformed the thrombi into bands. A congenital anomaly could be ruled out as the underlying cause of these structures. Pulmonary arteriosclerosis was the primary cause of the mural thrombi. There was no evidence of Ayerza's disease.

Katz, Louis N., and Ackerman, Walter: The Effect of the Heart's Position on the Electrocardiographic Appearance of Ventricular Extrasystoles. J. Clin. Investigation **11**: 1221, 1932.

Studies were made of the effect, in the open-chested anesthetized dog, of changing the heart's position on the electrocardiograms of induced extrasystoles. The shifts of the heart were (a) in an anteroposterior direction on the transverse axis at its base, (b) in a lateral direction on the anteroposterior axis at its base with practically no rotation on its long axis, and (c) rotation on its long axis (which runs from the base to apex) with some movement in a lateral direction on the anteroposterior axis at its base. The extrasystoles were induced in four regions, viz., the base and apex of the right and left ventricles.

The electrical axis of the various extrasystoles did not move the same amount nor always in the same direction when the heart was shifted. The electrical axis moved in the same direction as the anatomical axis in most types of beats when practically no rotation on the heart's own long axis accompanied the change in the heart's position. The electrical axis moved in a direction opposite to the anatomical axis in most types of beats when the heart was rotated on its own long axis at the same time.

Many times the direction of the major initial deflection of the extrasystoles was reversed in one or more leads.

The results are attributed to the unequal movements of the so-called three-dimensional vectors of the various extrasystoles when the heart was shifted. This resulted in an unequal and at times opposite movement of the projections of these three-dimensional vectors on the plane of the three leads.

The reversal in direction of the QRS group of ventricular extrasystoles, which often accompanied changes in the heart's position, shows (a) that the configuration and position of the heart cannot be ignored in analyzing the site of ventricular extrasystoles and bundle-branch block in man, and (b) that the direction of the QRS group of extrasystoles induced in the two patients reported with pericarditis and pericardial fistula may not be applied to the nondiseased human heart without consideration of the other factors involved.

On the basis of these results it would be unjustified to attempt to localize the site of ventricular extrasystoles or of bundle-branch block from the direction of the major initial complex in the three leads of the electrocardiogram.

Diamond, Mortimer: Calcification of the Myocardium in a Premature Infant. Arch. Path. **14**: 137, 1932.

In a twenty-six-week-old, premature infant, who lived with signs of cardiac failure for thirty minutes after birth, extensive calcification of the myocardium was found which is explained as secondary to toxic degeneration of the muscle fibers. The principal findings were in the right auricle which was rigid owing to the presence of yellowish white deposits which to a large extent had singled out the trabeculae carneae, making them appear as distinct, yellowish white linear bundles. The auricle measured 21 by 15 by 12 mm.; its wall was as much as 3 mm. in thickness, and its endocardium was smooth. On microscopic examination, there were extensive deposits of calcium in the right auricle which appeared in the form of coarse and branched trabeculae. In many places the calcification involved the entire thickness of the wall from the epicardium to the endocardium, which was markedly thickened. In the right auricular appendage practically all the muscle fibers had been substituted by calcium, and the derivation of the calcium trabeculae was clearly shown. Not only did the calcium trabeculae imitate the outlines of the muscle fibers, but they also showed their characteristic arrangement. There were some deposits of calcium in the left auricle, although they were less pronounced. Minor changes occurred elsewhere in the heart.

A review of the literature showed that calcification of the myocardium is secondary to preceding degeneration or necrosis of the muscle fibers. This degeneration may be due to vascular, inflammatory or toxic conditions. Fatty degeneration plays no part in calcification of the muscle fibers.

Ernstene, A. Carlton: The Anatomy and Physiology of Congenital Cardiovascular Disease. New England J. Med. **207**: 523, 1932.

The author divides congenital cardiovascular disease into three major groups: (1) the a-cyanotic group, (2) the group of cases having an arteriovenous shunt with possible transient cyanosis due to reversal of flow through the defect, and (3) the cyanotic group (morbus caeruleus), consisting principally of those congenital cardiac defects described as the tetralogy of Fallot, consisting of a defect of the ventricular septum, pulmonary or infundibular stenosis, dextroposition of the aorta and hypertrophy of the right ventricle.

Sprague, Howard B.: Congenital Heart Disease. New England J. Med. **207**: 525, 1932.

At the present time it is wiser, the author believes, to restrict attempts to the differential diagnosis of the anomalies in the congenital heart disease to the eight

types which are outlined in this paper. It is usually only confusing to think of all the possible combinations of congenital heart defects. If one can be sure of diagnosing the enumerated types, it may lead later to a better differentiation of the more obscure lesions which have not a characteristic combination of clinical signs.

Robey, William H.: Treatment of Rheumatic Heart Disease. New England J. Med. 207: 533, 1932.

In this symposium, the more commonly accepted methods of treatment for patients with this form of heart disease are briefly outlined. The control of pain by the use of salicylates and allied drugs, the eradication of foci of infection, particularly the tonsils, and other forms of treatment are mentioned. The author points out that the treatment of rheumatic heart disease during the course of fever is unnecessary and unsatisfactory. He states that one should not hurry into a diagnosis of cardiac lesion or lesions during the height of febrile attacks nor for several weeks after the cessation of fever. The rapidity of heart action plus edema about the valve orifices may distinctly obscure real lesions or simulate lesions in an otherwise normal heart. He states that digitalis is seldom indicated, for it is difficult to estimate its effect upon a heart during the tachycardia of any febrile state.

Breed, William B.: Diagnosis and Clinical Signs of Rheumatic Heart Disease in Children. New England J. Med. 207: 530, 1932.

This paper deals principally with the protein forms of the disease as it occurs in children. The author emphasizes the importance of fatigue, irritability, epistaxis, failure to gain weight and muscle pain. Vomiting, chorea, skin manifestations and nodules are also discussed.

Collis, W. R. F.: The Contagious Factor in the Etiology of Rheumatic Fever. Am. J. Dis. Child. 44: 485, 1932.

The author has observed an epidemic of nasopharyngeal infection in a group of twenty-five children, convalescing from rheumatism. In all, thirteen children were infected, and in eight of these an acute rheumatic relapse subsequently developed. Following a silent or incubation period of from seven to twenty-four days, various manifestations of rheumatism became manifest. The organism causing this epidemic was the hemolytic streptococcus, but it was only during the height of the throat infection that the organism could be obtained in anything like pure culture from the pharynx. Other epidemics of nasopharyngeal infection were observed in the same ward during this period. One of these was shown to be associated with pneumococcus and another with micrococcus catarrhalis; neither was followed by rheumatic relapses.

A study of these children was made by determining their skin sensitivity to streptococcus exotoxine consisting of a filtrate of a twenty-four-hour broth culture and the endotoxine which was an extract of the ground-up bodies of dried cocci. It was found that the children gave fewer positive reactions with the exotoxine than a similar age group of controls. When tested with the endotoxine, 100 per cent gave positive reactions compared with only 20 per cent of the controls. The author has also studied the incidence of acute streptococcus infections in a group of patients who had not previously had rheumatic fever. It is felt that there is no essential difference in the etiology of primary and secondary attacks of rheumatic fever. In conclusion, the author states that the etiology of rheumatic fever can be explained only when its connection with acute sore throat, caused by the hemolytic streptococcus is understood. It cannot be described as a contagious disease in the ordinary sense of the word, as more than one factor is responsible for its development. A streptococcal infection of the throat is no doubt contagious in the epidemic sense but is followed by rheumatic fever only in certain individuals.

Coburn, Alvin F., and Pauli, Ruth H.: Studies on the Relationship of Streptococcus Hemolyticus to the Rheumatic Process. 1. Observations on the Ecology of Hemolytic Streptococcus in Relation to the Epidemiology of Rheumatic Fever. J. Exper. Med. **56**: 609, 1932.

Certain factors of climate are favorable to streptococcus respiratory diseases. In those tropical environments where hemolytic streptococcus is unusual in the throat flora, scarlet fever is unknown and rheumatic fever rare. In New York City, however, following epidemic waves of pharyngitis with hemolytic streptococcus the incidence of rheumatic fever rises precipitously. The correlation between the geographical distribution of hemolytic streptococcus and rheumatic fever is a definite one.

Furthermore, in New York City during the seasons of the year in which hemolytic streptococcus is seldom recovered from the pharynx, acute attacks of rheumatism are unusual. Corresponding to the seasonal attacks of hemolytic streptococcus infections, the curve of incidence of acute rheumatism shows a similar form.

Among the children of wealthy patients, enjoying great protection, hemolytic streptococcus has been recovered infrequently from the throat, and rheumatism has not been encountered during this study. Among the poor under observation in New York City, however, the organisms is found frequently in the pharyngeal flora and rheumatic fever is common. The findings suggest that poverty and unhygienic living conditions favor both the activity of hemolytic streptococcus in the throat and the incidence of rheumatic fever.

Moreover, localized outbreaks of rheumatism have been observed frequently following epidemics of "sore throat." Bacteriological studies of these upper respiratory infections demonstrate a close relationship between the advent of hemolytic streptococcus in the throat flora and the outbreak of rheumatic fever in susceptible individuals.

In addition to these studies of streptococcus infections and their relationship to the development of rheumatic fever, observations of the rheumatic patient add further emphasis to this association. First, among the group of rheumatic children in an isolated environment, reactivation of the rheumatic process has been recognized only following the advent of hemolytic streptococcus in the throat flora.

Also, an investigation of families in which several members have rheumatic heart disease has led to the same conclusion. Recrudescences of the disease have been observed under a variety of conditions among these individuals. However, the one constant factor in the outbreaks of recrudescences in rheumatic homes is their association with family epidemics of hemolytic streptococcus infection.

Moreover, by studying rheumatic patients before, during and after transplantation to a tropical environment, it has been possible to demonstrate a close relationship between activity of the disease process and infection with hemolytic streptococcus. While the rheumatic patients remained in the tropics, this organism was not recovered from the pharyngeal flora, and the disease process seemed quiescent. On return to New York City, those individuals who have escaped respiratory infection have remained symptom-free. However, of those who have contracted hemolytic streptococcus pharyngitis, each has developed a rheumatic attack within three weeks after infection.

Finally, extensive bacteriological studies made in ambulatory rheumatic subjects over a period of four years have demonstrated that the individuals who escape respiratory disease remain free of rheumatic manifestations. On the other hand, the majority of rheumatic patients who contract hemolytic streptococcus pharyngitis experience shortly afterward a definite recrudescence of their disease. In conclusion, there is a close relationship between respiratory infection with hemolytic streptococcus and activity of the rheumatic process in susceptible individuals.

Coburn, Alvin F., and Pauli, Ruth H.: Studies on the Relationship of Streptococcus Hemolyticus to the Rheumatic Process. II. Observations on the Biological Character of Streptococcus Hemolyticus Associated With Rheumatic Disease. J. Exper. Med. **56**: 633, 1932.

To determine the nature of the organisms associated with outbreaks of rheumatism at the Pelham Home, in a large number of individuals at the Presbyterian Hospital Nurses' Training School and among rheumatic subjects in New York City under continuous clinical observation, studies of the throat flora have been conducted. Hemolytic streptococcus in most instances appeared in the pharynx from one to five weeks before the onset of the rheumatic attack. These organisms have been investigated with the usual types of bacteriological tests and, in addition, have been classified serologically according to Lancefield's technic. The results have demonstrated that the organisms were not of a single type but fell into six antigenic groups. The majority of the freshly isolated strains tested were strong toxin producers. The organisms producing the strongest toxin were cultures from the patients who developed extremely intense rheumatism. About 70 per cent of these toxins were neutralized by a monovalent streptococcus antiserum.

Coburn, Alvin F., and Pauli, Ruth H.: Studies on the Relationship of Streptococcus Hemolyticus to the Rheumatic Process. III. Observations on the Immunological Responses of Rheumatic Subjects to Hemolytic Streptococcus. J. Exper. Med. **56**: 651, 1932.

In the first two papers findings were presented which point to a close relationship between the incidence of rheumatic fever and the distribution of *Streptococcus hemolyticus*. The fact was emphasized that in the rheumatic subject a recrudescence of the disease process is usually preceded by pharyngeal infection with hemolytic streptococci. These organisms conspicuous in the throat flora during the period of infection preliminary to an attack of acute rheumatism fell into six antigenic groups and produced toxins which in 70 per cent were neutralized by a monovalent streptococcus antiserum. In the present study, four series of observations have been presented, demonstrating the development of immune bodies to hemolytic streptococcus during the course of rheumatic fever. The agglutination and complement fixation reactions of sera from patients with acute rheumatism suggest recent infection with streptococcus. Precipitin tests indicate that at the time of appearance of the rheumatic attack, individuals develop, in their blood, precipitins to the protein fractions of hemolytic streptococcus. That these precipitins may not be entirely specific is recognized from their cross-reactions with antigens of chemically related organisms. The studies made in association with E. W. Todd of England have demonstrated that at the onset of an attack of acute rheumatism, there occurs in each instance a rise in the antistreptolysin titer of the patient's serum. This titer is much higher than that observed in normal subjects or in patients with bacterial infection other than hemolytic streptococcus. This presence of antistreptolysin with an N.D. of 0.005 c.c. is considered strong evidence of recent infection by hemolytic streptococcus. In conclusion, the relationship between the incidence of hemolytic streptococcus and the geographical distribution of rheumatic fever, the relationship between the recrudescence in the rheumatic subject and infection of the throat with hemolytic streptococcus, the development of immune bodies for hemolytic streptococcus at the onset of the rheumatic attack, and the apparently specific relationship of antistreptolysin formation to infection with hemolytic streptococcus—together this combined evidence indicates that the infectious agent initiating the rheumatic process is *Streptococcus hemolyticus*.

Book Reviews

DIE BLUTDRUCKKRANKHEIT. By Prof. Dr. Otfried Müller and Prof. Dr. Walter Parrisius. Pp. 142, with 72 illustrations. Stuttgart, 1932, Ferdinand Enke.

In this volume Professor Müller, to whom the profession is already indebted for pioneer work in the application of Lombard's method of capillary microscopy in the living to clinical problems, and Professor Parrisius present a study of the hypertensive diseases. The scope of the investigation is indicated by the subtitle: "clinical, heredobiologic, anthropometric, biochemical, histological, capillary-microscopic, and other investigations on the circulation in hypertensive individuals."

Hypertensive disease is divided into three types:

1. Hypertension associated with inflammatory renal disease.
2. Essential hypertension without organic renal disease.
3. Hypertension associated with the arteriolosclerotic contracted kidney.

The fundamental separation of the second and third groups is surprising. The arteriolosclerotic kidney is generally regarded as an advanced stage of essential hypertension, and the reviewer is unable to see any evidence in the book that would tend to cast doubt on this well established view.

The three types were investigated from the point of view of their constitutional characteristics. It was found that nephritic hypertension occurs almost always in individuals of asthenic or "leptosome" habitus, and that evidences of endocrine dysfunction are absent. On the other hand, essential hypertension affects mostly persons of "pyknic" or sthenic habitus, who very often have such endocrine disturbances as obesity, diabetes, or menstrual disorders. In the third group of hypertension with arteriolosclerotic kidneys, both main constitutional types were almost equally represented. The hereditary factor is strong not only in essential but also in nephritic hypertension.

To American readers the most interesting part of the book will probably be the investigations on the capillaries. The capillaries of the bulbar conjunctiva, lip, breast, forearm, nail fold, thigh, and other parts were examined during life with the capillary microscope. Many beautiful photographs of the observations are reproduced. In essential hypertension the investigators find that the capillaries present a spastic-atonic picture, i. e., the arterial limb of the capillary is contracted and the venous limb relaxed and full of blood. It is the filling of the venous limb that accounts for the red appearance of these patients. In nephritic hypertension, on the other hand, the capillaries are contracted throughout their course, resulting in pallor. Another interesting observation is that the irritability of the capillaries to mechanical stimulation is increased in essential but not in nephritic hypertension.

The least satisfactory part of the book, to the reviewer, is that dealing with the endocrine disturbances in hypertension. The authors state that they observed changes in the morphology of the capillaries following the administration of thyroid, ovary, testis, or anterior lobe of the pituitary in patients presenting evidences of hypofunction of these glands. The gland preparations were given either by injection or by mouth. They also observed lowering of elevated blood pressure following administration of these endocrine products in appropriate cases. These results, especially with the oral administration of ovarian and testicular preparations, are contrary to general experience in this country, and in view of their great importance should be confirmed before acceptance. Nor does the authors' demonstration of "a tendency to increased tissue acidity" in essential hypertension seem unequivocal.

A. M. F.

LES TACHYCARDIES PAROXYSTIQUES VENTRICULAIRES. By Roger Fromet, Paris, 1932, with 541 pages, Masson et Cie.

The title, *Paroxysmal Ventricular Tachycardias*, suggests a slender volume of interest primarily to electrocardiographers; the study is, however, planned on broad lines and is distinctly clinical in viewpoint. Doctor Fromet considers ventricular tachycardia as the link which connects premature beats—either isolated or in salvos—on the one hand, with ventricular fibrillation on the other. He also discusses the relationship that often exists between ventricular tachycardia and heart-block or auricular fibrillation. He compares the benign and apparently idiopathic forms of the arrhythmia with those of grave import occurring after coronary thrombosis or in the presence of severe cardiac decompensation. He believes that in either case there is an irritative localized lesion of the bundle of His.

If the study is planned on broad lines, it is executed with careful attention to details. The arrangement is systematic and orderly; the argument is illustrated with numerous case histories, some reported in detail, and with well chosen electrocardiograms; italicized summaries emphasize the important points, and the bibliography is excellent.

Inasmuch as one usually considers ventricular tachycardia as an arrhythmia to be studied by graphic methods, the clinical emphasis is of special interest. Under the heading of *Diagnosis* (page 315) Doctor Fromet says that a tachycardia occurring in the presence of heart-block is almost certainly of ventricular origin; that in the presence of auricular fibrillation a rapid regular rate is due either to flutter or to ventricular tachycardia; that in coronary disease or severe decompensation a tachycardia is probably ventricular; and finally that ventricular tachycardia should be considered in the case of any unexplained tachycardia in an individual over fifty-five or sixty years. He believes (page 320) that the prognosis depends primarily on the underlying myocardial lesion but says that if the electrocardiographic tracing shows polymorphic complexes (in the discussion of left and right ventricular beats, one must remember that Doctor Fromet discounts the work of Barker, Macleod and Alexander and uses the classical terminology —see page 127), one must look for the onset of ventricular fibrillation and give a poor prognosis. He points out the fact that all drugs with the exception of quinidine may be useless or harmful and that quinidine is of little value when the myocardium is severely and permanently damaged. He also emphasizes the point that Stokes-Adams attacks are frequently due to transient ventricular tachycardia or fibrillation.

E. H.

THE CARDIAC OUTPUT OF MAN IN HEALTH AND DISEASE. By Arthur Grollman. 325 pages, Springfield and Baltimore, 1932, Charles C. Thomas.

In reviewing ideas, and the literature, nine years ago, concerning volume changes of the heart, Yandell Henderson observed that "The stroke volume of the heart is probably both for physiological and clinical purposes the most important quantitative function of the whole body." There can be little doubt that in the minds of physiologists from Harvey until the present day, the volume of the cardiac output has been regarded as a function of great significance. And that significance relates not to the behavior of the heart alone but to the much wider problem of the relation of the heart's output to the requirements of the body in nutrition and respiration. The use which Harvey made of his measurements of cardiac output is well known. The fact that Grollman begins his treatise with a mention of Harvey's experiments and speculations is evidence of his awareness of the historical importance which contributions to this problem in physiology possess. Grollman's investigations and the investigations of Marshall and Grollman come at the end, in a sense, of a long interest in this issue. How recent are their labors appears from the fact that Marshall's first papers on this subject appeared only six years ago (1926) and Grollman's not until 1928. Much has been accomplished in a brief period.

These researches would not alone, however, have provided the occasion for writing a monograph on "The Cardiac Output of Man in Health and Disease," as Grollman has done, had not the technic of analysis been advanced by his introducing the use of a new agent, acetylene, as an essential factor in his method. The long history of effort in the search for a satisfactory technic is described in detail by Grollman in the first fifty-one pages of his book. Beginning with the early estimates of Senac (1783), Thomas Young (1809), Haller (1757), and the later ones of Volkmann (1850), Edward Hering (1832), Vierordt (1858), Dogiel (1867) and Ludwig's pupils (Meade Smith, Stolnikow, Pawlow, Bohr), he recounts briefly those of Fick (1869-1870) and Hoorweg (1890), Stewart (1897-1921), Zuntz (1892-1898). He then describes the principle introduced by Fick in 1870, and the use which subsequent investigators have made of it. Gréhant and Quinquaud were the first (1886) to apply the principle in dogs. And the first direct estimations of the cardiac output in man were made in 1903 by Loewy and von Schrötter.

The list of those who have employed Fick's principle utilizing either oxygen or carbon dioxide is a long one, and the modifications which each has introduced have been numerous. The relative advantages of each of them as well as the difficulties and the errors inherent in them are analyzed critically and sometimes sharply. Grollman describes also the use of foreign gases, nitrogen, nitrous oxide, ethyl iodide and ethylene and defines both their usefulness and its absence. He criticizes also the various physical methods which have been suggested, the latest being that of Broemser and Ranke (1930) and finally the injection methods. Grollman's own method based on the use of acetylene is described in detail. The development of the method, the choice of this special gas, its fulfillment of the requirements of this particular situation, its solubility and diffusibility, its employment and the calculations which its use permits are all analyzed.

Proof that the acetylene method does in fact measure the cardiac output depends, of course, on the possibility of reproducing previous results, the logical coherence of the procedure and a reference to direct comparison, in this case, with the concentration of acetylene in the mixed venous and arterial bloods. The method seems so far to have satisfied the most rigid tests that have been applied to it. It has limitations; if the cardiac output exceeds 10 liters, the time occupied by a circuit of the blood is too short to permit a sufficient number of breaths to be drawn to mix thoroughly the air in the lungs with the acetylene in the bag. In consequence the blood flowing through the lungs may not enter into equilibrium with the gas. This difficulty Christensen may, meanwhile, have overcome. The other difficulty with the method applies to those clinical situations in which the respiratory apparatus is embarrassed to so great an extent as to interfere with proper mixture of the foreign gas with the air in the lungs.

It was Lindhard (1918) who first showed that the cardiac output bears a relation to the respiratory metabolism. Grollman has now demonstrated the close relationship between the basal metabolism and the cardiac output. Since the basal metabolism is proportional to the surface area, the step which Grollman next took seems logical; he related cardiac output to the surface area. A study of the measurements made so far of normal persons in a basal state shows that the cardiac output per square meter of body surface is 2.2 ± 3 liters per minute and that the average deviation from the mean is only 6.4 per cent.

To be able to make this statement is to announce one of the few important physiological constants observable in the human body. To do so is, as Henderson remarked, to supply exact information on probably "the most important quantitative function of the whole body." Considering the importance of the achievement, it is a pleasure to record the modesty which attends the original descriptions. Grollman has added a method of value, and he has also made a first rate contribution to physiological generalization.

Once in possession of a method apparently reliable, it has been possible to explore situations in which the cardiac output plays a part. In the brief period since 1929, many of them, both in health and in disease, have been studied. Differences in output according to age, especially after forty years, have not yet become known. But the influence of position, of the ingestion of food, of sleep, of sex (and the menstrual cycle), of psychic disturbances, of change in temperature and altitude, and of muscular exercise, have all been investigated, and in each case, with the addition of new light. The insight which knowing the cardiac output yields in learning the action of drugs, especially those which have an influence on the heart and the blood vessels, is, of course, of prime importance. Without knowing the cardiac output, precise knowledge is all but impossible. The action of alcohol, caffeine, and tobacco, or carbon dioxide, of digitalis, of drugs acting on the sympathetic system and of those originating in the organs of internal secretion have all been studied, in some cases so far, however, only in a preliminary way.

There are chapters also, dealing with the cardiac output in disease, in congenital heart disease, in the various heart and circulatory diseases of adult life and finally with its correlation with other physiological functions of the organism, such as metabolism, pulse rate, the velocity of the blood flow, the blood pressure and the size of the heart.

To describe the results of the investigations of these various matters would carry this description beyond the requirements of a review. They are in any case given with brevity and with clearness in the chapters themselves of this book.

Where there is so much to praise, the duty of calling attention to small blemishes is the more onerous. There are a few incorrect references in the early pages (Stewart on page 7, should read 433 instead of 423, Bauman and Lauter on page 11, should read 29 instead of 27, Loewy and von Schrötter on page 13 should read 320 instead of 32). The use of the word "determination," in accordance with a custom become all too common, is employed where "measurement" or "estimate" was formerly used. Where inquiry is being made, is there not something incongruous in using a word in which the operation of the will is, at least, intimated? "On" instead of "in" is also becoming usual in speaking of experiments or measurements in connection with animals or men, without corresponding increase in the beauty of the language. With the word data, a plural form, appears the adjective "this." "Boemser" is spelled without an r (page 175) and "die" is spelled with one (page 294, ref. 157). But on the credit side there are two pages (3 and 4) of terms accurately defined which should, because of their sensibleness, aid in dislodging many others which have encumbered the literature of this subject to its own confusion.

These are after all small matters. Of greater importance is the welcome which it is pleasure to accord a distinguished research.

A. E. C.